Vytorin—Cont.

Table 2
Response to VYTORIN after 5 Weeks in Patients with CHD or CHD Risk Equivalents and an LDL-C ≥130 mg/dL

	Simvastatin 20 mg	VYTORIN 10/10	VYTORIN 10/20	VYTORIN 10/40
N	253	251	109	97
Mean baseline LDL-C	174	165	167	171
Percent change LDL-C	−38	−47	−53	−59

In a multicenter, double-blind, 24-week, forced titration study, 788 patients with primary hypercholesterolemia, who had not met their NCEP ATP III target LDL-C goal, were randomized to receive coadministered ezetimibe and simvastatin equivalent to VYTORIN (10/10 and 10/20) or atorvastatin 10 mg. For all three treatment groups, the dose of the statin was titrated at 6-week intervals to 80 mg. At each pre-specified dose comparison, VYTORIN lowered LDL-C to a greater degree than atorvastatin (see Table 3).
[See table 3 at right]
In a multicenter, double-blind, 24-week trial, 214 patients with type 2 diabetes mellitus treated with thiazolidinediones (rosiglitazone or pioglitazone) for a minimum of 3 months and simvastatin 20 mg for a minimum of 6 weeks, were randomized to receive either simvastatin 40 mg or the coadministered active ingredients equivalent to VYTORIN 10/20. The median LDL-C and HbA1c levels at baseline were 89 mg/dL and 7.1%, respectively.
VYTORIN 10/20 was significantly more effective than doubling the dose of simvastatin to 40 mg. The median percent changes from baseline for VYTORIN vs simvastatin were: LDL-C -25% and -5%; total-C -16% and -5%; Apo B -19% and -5%; and non-HDL-C -23% and -5%. Results for HDL-C and TG between the two treatment groups were not significantly different.

Ezetimibe

In two multicenter, double-blind, placebo-controlled, 12-week studies in 1719 patients with primary hypercholesterolemia, ezetimibe significantly lowered total-C (-13%), LDL-C (-19%), Apo B (-14%), and TG (-8%), and increased HDL-C (+3%) compared to placebo. Reduction in LDL-C was consistent across age, sex, and baseline LDL-C.

Simvastatin

In two large, placebo-controlled clinical trials, the Scandinavian Simvastatin Survival Study (N=4,444 patients) and the Heart Protection Study (N=20,536 patients), the effects of treatment with simvastatin were assessed in patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease. Simvastatin was proven to reduce: the risk of total mortality by reducing CHD deaths; the risk of non-fatal myocardial infarction and stroke; and the need for coronary and non-coronary revascularization procedures.
No incremental benefit of VYTORIN on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established.

Homozygous Familial Hypercholesterolemia (HoFH)

A double-blind, randomized, 12-week study was performed in patients with a clinical and/or genotypic diagnosis of HoFH. Data were analyzed from a subgroup of patients (n=14) receiving simvastatin 40 mg at baseline. Increasing the dose of simvastatin from 40 to 80 mg (n=5) produced a reduction of LDL-C of 13% from baseline on simvastatin 40 mg. Coadministered ezetimibe and simvastatin equivalent to VYTORIN (10/40 and 10/80 pooled, n=9), produced a reduction of LDL-C of 23% from baseline on simvastatin 40 mg. In those patients coadministered ezetimibe and simvastatin equivalent to VYTORIN (10/80, n=5), a reduction of LDL-C of 29% from baseline on simvastatin 40 mg was produced.

INDICATIONS AND USAGE

Primary Hypercholesterolemia

VYTORIN is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and non- familial) hypercholesterolemia or mixed hyperlipidemia.

Homozygous Familial Hypercholesterolemia (HoFH)

VYTORIN is indicated for the reduction of elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.
Therapy with lipid-altering agents should be a component of multiple risk-factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid- altering agents should be used in addition to an appropriate diet (including restriction of saturated fat and cholesterol) and when the response to diet and other non-pharmacological measures has been inadequate. (See NCEP Adult Treatment Panel (ATP) III Guidelines, summarized in Table 4.)
[See table 4 at top of next page]

Table 1
Response to VYTORIN in Patients with Primary Hypercholesterolemia (Mean[a] % Change from Untreated Baseline[b])

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	HDL-C	TG[a]	Non-HDL-C
Pooled data (All VYTORIN doses)[c]	609	−38	−53	−42	+7	−24	−49
Pooled data (All simvastatin doses)[c]	622	−28	−39	−32	+7	−21	−36
Ezetimibe 10 mg	149	−13	−19	−15	+5	−11	−18
Placebo	148	−1	−2	0	0	−2	−2
VYTORIN by dose							
10/10	152	−31	−45	−35	+8	−23	−41
10/20	156	−36	−52	−41	+10	−24	−47
10/40	147	−39	−55	−44	+6	−23	−51
10/80	154	−43	−60	−49	+6	−31	−56
Simvastatin by dose							
10 mg	158	−23	−33	−26	+5	−17	−30
20 mg	150	−24	−34	−28	+7	−18	−32
40 mg	156	−29	−41	−33	+8	−21	−38
80 mg	158	−35	−49	−39	+7	−27	−45

[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] VYTORIN doses pooled (10/10-10/80) significantly reduced total-C, LDL-C, Apo B, TG, and non-HDL-C compared to simvastatin, and significantly increased HDL-C compared to placebo.

Table 3
Response to VYTORIN and Atorvastatin in Patients with Primary Hypercholesterolemia (Mean[a] % Change from Untreated Baseline[b])

Treatment	N	Total-C	LDL-C	Apo B	HDL-C	TG[a]	Non-HDL-C
Week 6							
Atorvastatin 10 mg[c]	262	−28	−37	−32	+5	−23	−35
VYTORIN 10/10[d]	263	−34[f]	−46[f]	−38[f]	+8[f]	−26	−43[f]
VYTORIN 10/20[e]	263	−36[f]	−50[f]	−41[f]	+10[f]	−25	−46[f]
Week 12							
Atorvastatin 20 mg	246	−33	−44	−38	+7	−28	−42
VYTORIN 10/20	250	−37[f]	−50[f]	−41[f]	+9	−28	−46[f]
VYTORIN 10/40	252	−39[f]	−54[f]	−45[f]	+12[f]	−31	−50[f]
Week 18							
Atorvastatin 40 mg	237	−37	−49	−42	+8	−31	−47
VYTORIN 10/40[g]	482	−40[f]	−56[f]	−45[f]	+11[f]	−32	−52[f]
Week 24							
Atorvastatin 80 mg	228	−40	−53	−45	+6	−35	−50
VYTORIN 10/80[g]	459	−43[f]	−59[f]	−49[f]	+12[f]	−35	−55[f]

[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] Atorvastatin: 10 mg start dose titrated to 20 mg, 40 mg, and 80 mg through Weeks 6, 12, 18, and 24
[d] VYTORIN: 10/10 start dose titrated to 10/20, 10/40, and 10/80 through Weeks 6, 12, 18, and 24
[e] VYTORIN: 10/20 start dose titrated to 10/40, 10/40, and 10/80 through Weeks 6, 12, 18, and 24
[f] $p \leq 0.05$ for difference with atorvastatin in the specified week
[g] Data pooled for common doses of VYTORIN at Weeks 18 and 24.

Prior to initiating therapy with VYTORIN, secondary causes for dyslipidemia (i.e., diabetes, hypothyroidism, obstructive liver disease, chronic renal failure, and drugs that increase LDL-C and decrease HDL-C [progestins, anabolic steroids, and corticosteroids]), should be excluded or, if appropriate, treated. A lipid profile should be performed to measure total-C, LDL-C, HDL-C and TG. For TG levels >400 mg/dL (>4.5 mmol/L), LDL-C concentrations should be determined by ultracentrifugation.
At the time of hospitalization for an acute coronary event, lipid measures should be taken on admission or within 24 hours. These values can guide the physician on initiation of LDL-lowering therapy before or at discharge.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.
Active liver disease or unexplained persistent elevations in serum transaminases (see WARNINGS, *Liver Enzymes*).
Pregnancy and lactation. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as simvastatin to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, VYTORIN is contraindicated during pregnancy and in nursing mothers. **VYTORIN should be administered to women of childbearing age only when such patients are highly unlikely to conceive.** If the patient becomes pregnant while taking this drug, VYTORIN should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus (see PRECAUTIONS, *Pregnancy*).

WARNINGS

Myopathy/Rhabdomyolysis

In clinical trials, there was no excess of myopathy or rhabdomyolysis associated with ezetimibe compared with the relevant control arm (placebo or HMG-CoA reductase inhibitor alone). However, myopathy and rhabdomyolysis are known adverse reactions to HMG-CoA reductase inhibitors and other lipid-lowering drugs. In clinical trials, the incidence of CK >10 X the upper limit of normal [ULN] was 0.2% for VYTORIN. (See PRECAUTIONS, *Skeletal Muscle.*)
Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase above 10 X ULN. Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglo-

binuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

- **Because VYTORIN contains simvastatin, the risk of myopathy/rhabdomyolysis is increased by concomitant use of VYTORIN with the following:**

Potent inhibitors of CYP3A4: Cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily), particularly with higher doses of VYTORIN (see CLINICAL PHARMACOLOGY, *Pharmacokinetics*; PRECAUTIONS, *Drug Interactions, CYP3A4 Interactions*).

Other drugs:

Gemfibrozil, particularly with higher doses of VYTORIN (see CLINICAL PHARMACOLOGY, *Pharmacokinetics*; PRECAUTIONS, *Drug Interactions, Interactions with lipid-lowering drugs that can cause myopathy when given alone*).

Other lipid-lowering drugs (other fibrates or ≥1 g/day of niacin) that can cause myopathy when given alone (see PRECAUTIONS, *Drug Interactions, Interactions with lipid-lowering drugs that can cause myopathy when given alone*).

Danazol particularly with higher doses of VYTORIN (see below: CLINICAL PHARMACOLOGY, *Pharmacokinetics*; PRECAUTIONS, *Drug Interactions, Other drug interactions*).

Amiodarone or verapamil with higher doses of VYTORIN (see PRECAUTIONS, *Drug Interactions, Other drug interactions*). In an ongoing clinical trial, myopathy has been reported in 6% of patients receiving simvastatin 80 mg and amiodarone. In an analysis of clinical trials involving 25,248 patients treated with simvastatin 20 to 80 mg, the incidence of myopathy was higher in patients receiving verapamil and simvastatin (4/635; 0.63%) than in patients taking simvastatin without a calcium channel blocker (13/21,224; 0.061%).

- **The risk of myopathy/rhabdomyolysis is dose related for simvastatin.** The incidence in clinical trials, in which patients were carefully monitored and some interacting drugs were excluded, has been approximately 0.02% at 20 mg, 0.07% at 40 mg and 0.3% at 80 mg.

Consequently:

1. **Use of VYTORIN concomitantly with itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily) should be avoided.** If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with VYTORIN should be suspended during the course of treatment. Concomitant use with other medicines labeled as having a potent inhibitory effect on CYP3A4 at therapeutic doses should be avoided unless the benefits of combined therapy outweigh the increased risk.
2. There is an increased risk of myopathy when simvastatin is used concomitantly with gemfibrozil or other fibrates; the safety and effectiveness of ezetimibe administered with fibrates have not been established. **Therefore, the concomitant use of VYTORIN and fibrates should be avoided.** (See PRECAUTIONS, *Drug Interactions, Other Drug Interactions, Fibrates*.)
3. Caution should be used when prescribing lipid-lowering doses (≥1 g/day) of niacin with VYTORIN, as niacin can cause myopathy when given alone. **The benefit of further alterations in lipid levels by the combined use of VYTORIN with niacin should be carefully weighed against the potential risks of this drug combination.**
4. **The dose of VYTORIN should not exceed 10/10 mg daily in patients receiving concomitant medication with cyclosporine or danazol.** The benefits of the use of VYTORIN in patients receiving cyclosporine or danazol should be carefully weighed against the risks of these combinations. **(See PRECAUTIONS, *Drug Interactions, Other Drug Interactions, Cyclosporine*.)**
5. **The dose of VYTORIN should not exceed 10/20 mg daily in patients receiving concomitant medication with amiodarone or verapamil. The combined use of VYTORIN at doses higher than 10/20 mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy.**
6. **All patients starting therapy with VYTORIN, or whose dose of VYTORIN is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. VYTORIN therapy should be discontinued immediately if myopathy is diagnosed or suspected.** The presence of these symptoms, and/or a CK level >10 times the ULN indicates myopathy. In most cases, when patients were promptly discontinued from simvastatin treatment, muscle symptoms and CK increases resolved. Periodic CK determinations may be considered in patients starting therapy with VYTORIN or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.
7. Many of the patients who have developed rhabdomyolysis on therapy with simvastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients taking VYTORIN merit closer monitoring. Therapy with VYTORIN should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

Liver Enzymes

In three placebo-controlled, 12-week trials, the incidence of consecutive elevations (≥3 X ULN) in serum transaminases was 1.7% overall for patients treated with VYTORIN and appeared to be dose-related with an incidence of 2.6% for patients treated with VYTORIN 10/80. In controlled long-term (48-week) extensions, which included both newly-treated and previously-treated patients, the incidence of consecutive elevations (≥3 X ULN) in serum transaminases was 1.8% overall and 3.6% for patients treated with VYTORIN 10/80. These elevations in transaminases were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment.

It is recommended that liver function tests be performed before the initiation of treatment with VYTORIN, and thereafter when clinically indicated. Patients titrated to the 10/80-mg dose should receive an additional test prior to titration, 3 months after titration to the 10/80-mg dose, and periodically thereafter (e.g., semiannually) for the first year of treatment. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of 3 X ULN or greater persist, withdrawal of therapy with VYTORIN is recommended.

VYTORIN should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained persistent transaminase elevations are contraindications to the use of VYTORIN.

Table 4
Summary of NCEP ATP III Guidelines

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes[a] (mg/dL)	LDL level at Which to Consider Drug Therapy (mg/dL)
CHD or CHD risk equivalents[b] (10-year risk >20%)[c]	<100	≥100	≥130 (100-129: drug optional)[d]
2+ Risk factors[e] (10-year risk ≤20%)[c]	<130	≥130	10-year risk 10–20%: ≥130[c] 10-year risk <10%: ≥160[c]
0–1 Risk factor[f]	<160	≥160	≥190 (160–189: LDL-lowering drug optional)

[a] Therapeutic lifestyle changes include: 1) dietary changes: reduced intake of saturated fats (<7% of total calories) and cholesterol (<200 mg per day), and enhancing LDL lowering with plant stanols/sterols (2 g/d) and increased viscous (soluble) fiber (10–25 g/d), 2) weight reduction, and 3) increased physical activity.

[b] CHD risk equivalents comprise: diabetes, multiple risk factors that confer a 10-year risk for CHD >20%, and other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm and symptomatic carotid artery disease).

[c] Risk assessment for determining the 10-year risk for developing CHD is carried out using the Framingham risk scoring. Refer to JAMA, May 16, 2001; 285 (19): 2486–2497, or the NCEP website (http://www.nhlbi.nih.gov) for more details.

[d] Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

[e] Major risk factors (exclusive of LDL cholesterol) that modify LDL goals include cigarette smoking, hypertension (BP ≥140/90 mm Hg or on anti-hypertensive medication), low HDL cholesterol (<40 mg/dL), family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years), age (men ≥45 years; women ≥55 years). HDL cholesterol ≥60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count.

[f] Almost all people with 0-1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

PRECAUTIONS

Information for Patients

Patients should be advised about substances they should not take concomitantly with VYTORIN and be advised to report promptly unexplained muscle pain, tenderness, or weakness (see list below and WARNINGS, *Myopathy/Rhabdomyolysis*). Patients should also be advised to inform other physicians prescribing a new medication that they are taking VYTORIN.

Skeletal Muscle

In post-marketing experience with ezetimibe, cases of myopathy and rhabdomyolysis have been reported regardless of causality. Most patients who developed rhabdomyolysis were taking a statin prior to initiating ezetimibe. However, rhabdomyolysis has been reported very rarely with ezetimibe monotherapy and very rarely with the addition of ezetimibe to agents known to be associated with increased risk of rhabdomyolysis, such as fibrates.

Hepatic Insufficiency

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, VYTORIN is not recommended in these patients. (See CLINICAL PHARMACOLOGY, *Pharmacokinetics, Special Populations*.)

***Drug Interactions* (See also CLINICAL PHARMACOLOGY, Drug Interactions)**

VYTORIN

CYP3A4 Interactions

Potent inhibitors of CYP3A4 (below) increase the risk of myopathy by reducing the elimination of the simvastatin component of VYTORIN.

See WARNINGS, *Myopathy/Rhabdomyolysis*, and CLINICAL PHARMACOLOGY, *Pharmacokinetics, Drug Interactions*.

Itraconazole
Ketoconazole
Erythromycin
Clarithromycin
Telithromycin
HIV protease inhibitors
Nefazodone
Cyclosporine
Large quantities of grapefruit juice (>1 quart daily)

Interactions with lipid-lowering drugs that can cause myopathy when given alone

See WARNINGS, *Myopathy/Rhabdomyolysis*.

The risk of myopathy is increased by gemfibrozil and to a lesser extent by other fibrates and niacin (nicotinic acid) (≥1 g/day).

Other drug interactions

Danazol: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of danazol particularly with higher doses of VYTORIN (see CLINICAL PHARMACOLOGY, *Pharmacokinetics*; WARNINGS, *Myopathy/Rhabdomyolysis*).

Amiodarone or Verapamil: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone or verapamil with higher doses of VYTORIN (see WARNINGS, *Myopathy/Rhabdomyolysis*).

Cholestyramine: Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe approximately 55%. The incremental LDL-C reduction due to adding VYTORIN to cholestyramine may be reduced by this interaction.

Cyclosporine: Caution should be exercised when using VYTORIN and cyclosporine concomitantly due to increased exposure to both ezetimibe and cyclosporine. Cyclosporine concentrations should be monitored in patients receiving VYTORIN and cyclosporine.

The degree of increase in ezetimibe exposure may be greater in patients with severe renal insufficiency. In patients treated with cyclosporine, the potential effects of the increased exposure to ezetimibe from concomitant use should be carefully weighed against the benefits of alterations in lipid levels provided by ezetimibe. In a pharmacokinetic study in post-renal transplant patients with mildly impaired or normal renal function (creatinine clearance of >50 mL/min), concomitant cyclosporine administration increased the mean AUC and C_{max} of total ezetimibe 3.4-fold (range 2.3- to 7.9-fold) and 3.9-fold (range 3.0- to 4.4-fold), respectively. In a separate study, the total ezetimibe exposure increased 12-fold in one renal transplant patient with severe renal insufficiency receiving multiple medications, including cyclosporine. (See CLINICAL PHARMACOLOGY, *Drug Interactions* and WARNINGS, *Myopathy/Rhabdomyolysis*.)

Digoxin: Concomitant administration of a single dose of digoxin in healthy male volunteers receiving simvastatin resulted in a slight elevation (less than 0.3 ng/mL) in plasma digoxin concentrations compared to concomitant administration of placebo and digoxin. Patients taking digoxin should be monitored appropriately when VYTORIN is initiated.

Fibrates: The safety and effectiveness of VYTORIN administered with fibrates have not been established.

Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile (see ANIMAL PHARMACOLOGY). Coadministration of VYTORIN with fibrates is not recommended until use in patients is studied. (See WARNINGS, *Myopathy/Rhabdomyolysis*.)

Warfarin: Simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), in-

Continued on next page

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creased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in a normal volunteer study and in a hypercholesterolemic patient study, respectively. With other statins, clinically evident bleeding and/or increased prothrombin time has been reported in a few patients taking coumarin anticoagulants concomitantly. In such patients, prothrombin time should be determined before starting VYTORIN and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of VYTORIN is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males. There have been post-marketing reports of increased International Normalized Ratio (INR) in patients who had ezetimibe added to warfarin. Most of these patients were also on other medications.

The effect of VYTORIN on the prothrombin time has not been studied.

Ezetimibe

Fenofibrate: In a pharmacokinetic study, concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold.

Gemfibrozil: In a pharmacokinetic study, concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1.7-fold.

Simvastatin

Propranolol: In healthy male volunteers there was a significant decrease in mean C_{max}, but no change in AUC, for simvastatin total and active inhibitors with concomitant administration of single doses of simvastatin and propranolol. The clinical relevance of this finding is unclear. The pharmacokinetics of the enantiomers of propranolol were not affected.

CNS Toxicity

Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 12 times higher than the mean plasma drug level in humans taking 80 mg/day.

A chemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean plasma drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels were seen in dogs treated with simvastatin at a dose of 360 mg/kg/day, a dose that produced mean plasma drug levels that were about 14 times higher than the mean plasma drug levels in humans taking 80 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class.

There were cataracts in female rats after two years of treatment with 50 and 100 mg/kg/day (22 and 25 times the human AUC at 80 mg/day, respectively) and in dogs after three months at 90 mg/kg/day (19 times) and at two years at 50 mg/kg/day (5 times).

Carcinogenesis, Mutagenesis, Impairment of Fertility

VYTORIN

No animal carcinogenicity or fertility studies have been conducted with the combination of ezetimibe and simvastatin. The combination of ezetimibe with simvastatin did not show evidence of mutagenicity *in vitro* in a microbial mutagenicity (Ames) test with *Salmonella typhimurium* and *Escherichia coli* with or without metabolic activation. No evidence of clastogenicity was observed *in vitro* in a chromosomal aberration assay in human peripheral blood lymphocytes with ezetimibe and simvastatin with or without metabolic activation. There was no evidence of genotoxicity at doses up to 600 mg/kg with the combination of ezetimibe and simvastatin (1:1) in the *in vivo* mouse micronucleus test.

Ezetimibe

A 104-week dietary carcinogenicity study with ezetimibe was conducted in rats at doses up to 1500 mg/kg/day (males) and 500 mg/kg/day (females) (~20 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe). A 104-week dietary carcinogenicity study with ezetimibe was also conducted in mice at doses up to 500 mg/kg/day (>150 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe). There were no statistically significant increases in tumor incidences in drug-treated rats or mice.

No evidence of mutagenicity was observed *in vitro* in a microbial mutagenicity (Ames) test with *Salmonella typhimurium* and *Escherichia coli* with or without metabolic activation. No evidence of clastogenicity was observed *in vitro* in a chromosomal aberration assay in human peripheral blood lymphocytes with or without metabolic activation. In addition, there was no evidence of genotoxicity in the *in vivo* mouse micronucleus test.

In oral (gavage) fertility studies of ezetimibe conducted in rats, there was no evidence of reproductive toxicity at doses up to 1000 mg/kg/day in male or female rats (~7 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe).

Simvastatin

In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 1, 4, and 8 times higher than the mean human plasma drug level, respectively (as total inhibitory activity based on AUC) after an 80-mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day.

In a separate 92-week carcinogenicity study in mice at doses up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed (mean plasma drug levels were 1 times higher than humans given 80 mg simvastatin as measured by AUC).

In a two-year study in rats at 25 mg/kg/day, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 11 times higher levels of simvastatin than in humans given 80 mg simvastatin (as measured by AUC).

A second two-year rat carcinogenicity study with doses of 50 and 100 mg/kg/day produced hepatocellular adenomas and carcinomas (in female rats at both doses and in males at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and females at both doses; thyroid follicular cell carcinomas were increased in females at 100 mg/kg/day. The increased incidence of thyroid neoplasms appears to be consistent with findings from other HMG-CoA reductase inhibitors. These treatment levels represented plasma drug levels (AUC) of approximately 7 and 15 times (males) and 22 and 25 times (females) the mean human plasma drug exposure after an 80 milligram daily dose.

No evidence of mutagenicity was observed in a microbial mutagenicity (Ames) test with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (4 times the maximum human exposure level, based on AUC, in patients receiving 80 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day, (which produces exposure levels 22 times higher than those in humans taking 80 mg/day based on surface area, mg/m^2), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation at 10 mg/kg/day, (approximately 2 times the human exposure, based on AUC, at 80 mg/day). The clinical significance of these findings is unclear.

Pregnancy

Pregnancy Category: X

See CONTRAINDICATIONS.

VYTORIN

As safety in pregnant women has not been established, treatment should be immediately discontinued as soon as pregnancy is recognized. VYTORIN should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.

Ezetimibe

In oral (gavage) embryo-fetal development studies of ezetimibe conducted in rats and rabbits during organogenesis, there was no evidence of embryolethal effects at the doses tested (250, 500, 1000 mg/kg/day). In rats, increased incidences of common fetal skeletal findings (extra pair of thoracic ribs, unossified cervical vertebral centra, shortened ribs) were observed at 1000 mg/kg/day (~10 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe). In rabbits treated with ezetimibe, an increased incidence of extra thoracic ribs was observed at 1000 mg/kg/day (150 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe). Ezetimibe crossed the placenta when pregnant rats and rabbits were given multiple oral doses.

Multiple-dose studies of ezetimibe coadministered with HMG-CoA reductase inhibitors (statins) in rats and rabbits during organogenesis result in higher ezetimibe and statin exposures. Reproductive findings occur at lower doses in coadministration therapy compared to monotherapy.

Simvastatin

Simvastatin was not teratogenic in rats at doses of 25 mg/kg/day or in rabbits at doses up to 10 mg/kg daily. These doses resulted in 3 times (rat) or 3 times (rabbit) the human exposure based on mg/m^2 surface area. However, in studies with another structurally-related HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice.

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. In a review[2] of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or another structurally related HMG-CoA reductase inhibitor, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a 3- to 4-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified.

Labor and Delivery

The effects of VYTORIN on labor and delivery in pregnant women are unknown.

Nursing Mothers

In rat studies, exposure to ezetimibe in nursing pups was up to half of that observed in maternal plasma. It is not known whether ezetimibe or simvastatin are excreted into human breast milk. Because a small amount of another drug in the same class as simvastatin is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women who are nursing should not take VYTORIN (see CONTRAINDICATIONS).

Pediatric Use

VYTORIN

There are insufficient data for the safe and effective use of VYTORIN in pediatric patients. (See *Ezetimibe* and *Simvastatin* below.)

Ezetimibe

The pharmacokinetics of ezetimibe in adolescents (10 to 18 years) have been shown to be similar to that in adults. Treatment experience with ezetimibe in the pediatric population is limited to 4 patients (9 to 17 years) with homozygous sitosterolemia and 5 patients (11 to 17 years) with HoFH. Treatment with ezetimibe in children (<10 years) is not recommended.

Simvastatin

Safety and effectiveness of simvastatin in patients 10–17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial in adolescent boys and in girls who were at least 1 year postmenarche. Patients treated with simvastatin had an adverse experience profile generally similar to that of patients treated with placebo. **Doses greater than 40 mg have not been studied in this population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. Adolescent females should be counseled on appropriate contraceptive methods while on therapy with simvastatin (see CONTRAINDICATIONS and PRECAUTIONS, *Pregnancy*). Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-menarchal girls.

Geriatric Use

Of the patients who received VYTORIN in clinical studies, 792 were 65 and older (this included 176 who were 75 and older). The safety of VYTORIN was similar between these patients and younger patients. Greater sensitivity of some older individuals cannot be ruled out. (See CLINICAL PHARMACOLOGY, *Special Populations* and ADVERSE REACTIONS.)

[2] Manson, J.M., Freyssinges, C., Ducrocq, M.B., Stephenson, W.P., Postmarketing Surveillance of Lovastatin and Simvastatin Exposure During Pregnancy, *Reproductive Toxicology*, 10(6):439–446, 1996.

ADVERSE REACTIONS

VYTORIN has been evaluated for safety in more than 3800 patients in clinical trials. VYTORIN was generally well tolerated.

Table 5 summarizes the frequency of clinical adverse experiences reported in ≥2% of patients treated with VYTORIN (n=1236) and at an incidence greater than placebo regardless of causality assessment from three similarly designed, placebo-controlled trials.

[See table 5 at top of next page]

Post-marketing Experience

The adverse reactions reported for VYTORIN are consistent with those previously reported with ezetimibe and/or simvastatin.

Ezetimibe

Other adverse experiences reported with ezetimibe in placebo-controlled studies, regardless of causality assessment: *Body as a whole – general disorders:* fatigue; *Gastrointestinal system disorders:* abdominal pain, diarrhea; *Infection and infestations:* infection viral, pharyngitis, sinusitis; *Musculoskeletal system disorders:* arthralgia, back pain; *Respiratory system disorders:* coughing.

Post-marketing Experience

The following adverse reactions have been reported in post-marketing experience, regardless of causality assessment: Hypersensitivity reactions, including angioedema and rash; elevated creatine phosphokinase; elevations in liver trans-

aminases; hepatitis; thrombocytopenia; pancreatitis; nausea; cholelithiasis; cholecystitis; and, very rarely, myopathy/rhabdomyolysis (see WARNINGS, *Myopathy/Rhabdomyolysis*).

Simvastatin

Other adverse experiences reported with simvastatin in placebo-controlled clinical studies, regardless of causality assessment: *Body as a whole – general disorders:* asthenia; *Eye disorders:* cataract; *Gastrointestinal system disorders:* abdominal pain, constipation, diarrhea, dyspepsia, flatulence, nausea; *Skin and subcutaneous tissue disorders:* eczema, pruritus, rash.

The following effects have been reported with other HMG-CoA reductase inhibitors. Not all the effects listed below have necessarily been associated with simvastatin therapy. *Musculoskeletal system disorders:* muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgias.

Nervous system disorders: dysfunction of certain cranial nerves (including alteration of taste, impairment of extraocular movement, facial paresis), tremor, dizziness, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances.

Ear and labyrinth disorders: vertigo.

Psychiatric disorders: anxiety, insomnia, depression, loss of libido.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia; leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal system disorders: pancreatitis, vomiting.

Hepatobiliary disorders: hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma.

Metabolism and nutrition disorders: anorexia.

Skin and subcutaneous tissue disorders: alopecia, pruritus. A variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.

Reproductive system and breast disorders: gynecomastia, erectile dysfunction.

Eye disorders: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

Laboratory Tests

Marked persistent increases of serum transaminases have been noted (see WARNINGS, *Liver Enzymes*). About 5% of patients taking simvastatin had elevations of CK levels of 3 or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CK. Muscle pain or dysfunction usually was not reported (see WARNINGS, *Myopathy/Rhabdomyolysis*).

Concomitant Lipid-Lowering Therapy

In controlled clinical studies in which simvastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with simvastatin or cholestyramine.

Adolescent Patients (ages 10–17 years)

In a 48-week controlled study in adolescent boys and girls who were at least 1 year post-menarche, 10–17 years of age with heterozygous familial hypercholesterolemia (n=175), the safety and tolerability profile of the group treated with simvastatin (10–40 mg daily) was generally similar to that of the group treated with placebo, with the most common adverse experiences observed in both groups being upper respiratory infection, headache, abdominal pain, and nausea (see CLINICAL PHARMACOLOGY, *Special Populations* and PRECAUTIONS, *Pediatric Use*).

OVERDOSAGE

VYTORIN

No specific treatment of overdosage with VYTORIN can be recommended. In the event of an overdose, symptomatic and supportive measures should be employed.

Ezetimibe

In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, or 40 mg/day to 18 patients with primary hypercholesterolemia for up to 56 days, was generally well tolerated.

A few cases of overdosage have been reported; most have not been associated with adverse experiences. Reported adverse experiences have not been serious.

Simvastatin

A few cases of overdosage with simvastatin have been reported; the maximum dose taken was 3.6 g. All patients recovered without sequelae.

The dialyzability of simvastatin and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving VYTORIN and should continue on this diet during treatment with VYTORIN. The dosage should be individualized according to the baseline LDL-C level, the recommended goal of therapy, and the patient's response. (See NCEP Adult Treatment Panel (ATP) III Guidelines, summarized in Table 4.) VYTORIN should be taken as a single daily dose in the evening, with or without food.

Table 5*
Clinical Adverse Events Occurring in ≥2% of Patients Treated with VYTORIN and at an Incidence Greater than Placebo, Regardless of Causality

Body System/Organ Class Adverse Event	Placebo (%) n=311	Ezetimibe 10 mg (%) n=302	Simvastatin** (%) n=1234	VYTORIN** (%) n=1236
Body as a whole – general disorders				
Headache	6.4	6.0	5.9	6.8
Infection and infestations				
Influenza	1.0	1.0	1.9	2.6
Upper respiratory tract infection	2.6	5.0	5.0	3.9
Musculoskeletal and connective tissue disorders				
Myalgia	2.9	2.3	2.6	3.5
Pain in extremity	1.3	3.0	2.0	2.3

*Includes two placebo-controlled combination studies in which the active ingredients equivalent to VYTORIN were coadministered and one placebo-controlled study in which VYTORIN was administered.
**All doses.

The dosage range is 10/10 mg/day through 10/80 mg/day. The recommended usual starting dose is 10/20 mg/day. Initiation of therapy with 10/10 mg/day may be considered for patients requiring less aggressive LDL-C reductions. Patients who require a larger reduction in LDL-C (greater than 55%) may be started at 10/40 mg/day. After initiation or titration of VYTORIN, lipid levels may be analyzed after 2 or more weeks and dosage adjusted, if needed. See below for dosage recommendations for patients receiving certain concomitant therapies and for those with renal insufficiency.

Patients with Homozygous Familial Hypercholesterolemia

The recommended dosage for patients with homozygous familial hypercholesterolemia is VYTORIN 10/40 mg/day or 10/80 mg/day in the evening. VYTORIN should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

Patients with Hepatic Insufficiency

No dosage adjustment is necessary in patients with mild hepatic insufficiency (see PRECAUTIONS, *Hepatic Insufficiency*).

Patients with Renal Insufficiency

No dosage adjustment is necessary in patients with mild or moderate renal insufficiency. However, for patients with severe renal insufficiency, VYTORIN should not be started unless the patient has already tolerated treatment with simvastatin at a dose of 5 mg or higher. Caution should be exercised when VYTORIN is administered to these patients and they should be closely monitored (see CLINICAL PHARMACOLOGY, *Pharmacokinetics* and WARNINGS, *Myopathy/Rhabdomyolysis*).

Geriatric Patients

No dosage adjustment is necessary in geriatric patients (see CLINICAL PHARMACOLOGY, *Special Populations*).

Coadministration with Bile Acid Sequestrants

Dosing of VYTORIN should occur either ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant (see PRECAUTIONS, *Drug Interactions*).

Patients taking Cyclosporine or Danazol

Caution should be exercised when initiating VYTORIN in the setting of cyclosporine. In patients taking cyclosporine or danazol, VYTORIN should not be started unless the patient has already tolerated treatment with simvastatin at a dose of 5 mg or higher. The dose of VYTORIN should not exceed 10/10 mg/day.

Patients taking Amiodarone or Verapamil

In patients taking amiodarone or verapamil concomitantly with VYTORIN, the dose should not exceed 10/20 mg/day (see WARNINGS, *Myopathy/Rhabdomyolysis* and PRECAUTIONS, *Drug Interactions, Other drug interactions*).

HOW SUPPLIED

No. 3873 — Tablets VYTORIN 10/10 are white to off-white capsule-shaped tablets with code "311" on one side.
They are supplied as follows:
NDC 66582-311-31 bottles of 30
NDC 66582-311-54 bottles of 90
NDC 66582-311-82 bottles of 1000 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)
NDC 66582-311-87 bottles of 10,000 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)
NDC 66582-311-28 unit dose packages of 100.

No. 3874 — Tablets VYTORIN 10/20 are white to off-white capsule-shaped tablets with code "312" on one side.
They are supplied as follows:
NDC 66582-312-31 bottles of 30
NDC 66582-312-54 bottles of 90
NDC 66582-312-82 bottles of 1000 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)
NDC 66582-312-87 bottles of 10,000 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)
NDC 66582-312-28 unit dose packages of 100.

No. 3875 — Tablets VYTORIN 10/40 are white to off-white capsule-shaped tablets with code "313" on one side.
They are supplied as follows:
NDC 66582-313-31 bottles of 30
NDC 66582-313-54 bottles of 90
NDC 66582-313-74 bottles of 500 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)
NDC 66582-313-52 unit dose packages of 50.

No. 3876 — Tablets VYTORIN 10/80 are white to off-white capsule-shaped tablets with code "315" on one side.
They are supplied as follows:
NDC 66582-315-31 bottles of 30
NDC 66582-315-54 bottles of 90
NDC 66582-315-74 bottles of 500 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)
NDC 66582-315-52 unit dose packages of 50.

Storage

Store at 20–25°C (68–77°F). [See USP Controlled Room Temperature.] Keep container tightly closed.

Storage of 10,000 count bottles

Store bottle of 10,000 VYTORIN 10/10 and 10/20 capsule-shaped tablets at 20–25° C (68–77° F). [See USP Controlled Room Temperature.] Store in original container until time of use. When product container is subdivided, repackage into a tightly-closed, light-resistant container. Entire contents must be repackaged immediately upon opening.

9619603
Issued March 2005
Printed in USA
MERCK/Schering-Plough Pharmaceuticals
Manufactured for:
MERCK/Schering-Plough Pharmaceuticals
North Wales, PA 19454, USA
By:
MSD Technology Singapore Pte. Ltd.
Singapore 637766
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VYTORIN™ (ezetimibe/simvastatin) Tablets

Patient Information about VYTORIN (VI-tor-in)

Generic name: ezetimibe/simvastatin tablets

Read this information carefully before you start taking VYTORIN. Review this information each time you refill your prescription for VYTORIN as there may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about VYTORIN, ask your doctor. Only your doctor can determine if VYTORIN is right for you.

What is VYTORIN?

VYTORIN contains two cholesterol-lowering medications, ezetimibe and simvastatin, available as a tablet in four strengths:
— VYTORIN 10/10 (ezetimibe 10 mg/simvastatin 10 mg)
— VYTORIN 10/20 (ezetimibe 10 mg/simvastatin 20 mg)
— VYTORIN 10/40 (ezetimibe 10 mg/simvastatin 40 mg)
— VYTORIN 10/80 (ezetimibe 10 mg/simvastatin 80 mg)

VYTORIN is a medicine used to lower levels of total cholesterol, LDL (bad) cholesterol, and fatty substances called triglycerides in the blood. In addition, VYTORIN raises levels of HDL (good) cholesterol. It is used for patients who cannot control their cholesterol levels by diet alone. You should stay on a cholesterol-lowering diet while taking this medicine.

VYTORIN works to reduce your cholesterol in two ways. It reduces the cholesterol absorbed in your digestive tract, as well as the cholesterol your body makes by itself. VYTORIN does not help you lose weight.

For more information about cholesterol, see the section called "What should I know about high cholesterol?"

Who should not take VYTORIN?

Do not take VYTORIN:
- If you are allergic to ezetimibe or simvastatin, the active ingredients in VYTORIN, or to the inactive ingredients. For a list of inactive ingredients, see the "Inactive ingredients" section at the end of this information sheet.
- If you have active liver disease or repeated blood tests indicating possible liver problems.
- If you are pregnant, or think you may be pregnant, or planning to become pregnant or breast-feeding.

Continued on next page

Vytorin—Cont.

VYTORIN is not recommended for use in children under 10 years of age.

What should I tell my doctor before and while taking VYTORIN?

Tell your doctor right away if you experience unexplained muscle pain, tenderness, or weakness. This is because on rare occasions, muscle problems can be serious, including muscle breakdown resulting in kidney damage.

The risk of muscle breakdown is greater at higher doses of VYTORIN.

The risk of muscle breakdown is greater in patients with kidney problems.

Taking VYTORIN with certain substances can increase the risk of muscle problems. It is particularly important to tell your doctor if you are taking any of the following:

- cyclosporine
- danazol
- antifungal agents (such as itraconazole or ketoconazole)
- fibric acid derivatives (such as gemfibrozil, bezafibrate, or fenofibrate)
- the antibiotics erythromycin, clarithromycin, and telithromycin
- HIV protease inhibitors (such as indinavir, nelfinavir, ritonavir, and saquinavir)
- the antidepressant nefazodone
- amiodarone (a drug used to treat an irregular heartbeat)
- verapamil (a drug used to treat high blood pressure, chest pain associated with heart disease, or other heart conditions)
- large doses (≥1 g/day) of niacin or nicotinic acid
- large quantities of grapefruit juice (>1 quart daily)

It is also important to tell your doctor if you are taking coumarin anticoagulants (drugs that prevent blood clots, such as warfarin).

Tell your doctor about any prescription and nonprescription medicines you are taking or plan to take, including natural or herbal remedies.

Tell your doctor about all your medical conditions including allergies.

Tell your doctor if you:

- drink substantial quantities of alcohol or ever had liver problems. VYTORIN may not be right for you.
- are pregnant or plan to become pregnant. Do not use VYTORIN if you are pregnant, trying to become pregnant or suspect that you are pregnant. If you become pregnant while taking VYTORIN, stop taking it and contact your doctor immediately.
- are breast-feeding. Do not use VYTORIN if you are breast-feeding.

Tell other doctors prescribing a new medication that you are taking VYTORIN.

How should I take VYTORIN?

Your doctor has prescribed your dose of VYTORIN. The available doses of VYTORIN are 10/10, 10/20, 10/40, and 10/80. The usual daily starting dose is VYTORIN 10/20.

- Take VYTORIN once a day, in the evening, with or without food.
- Try to take VYTORIN as prescribed. If you miss a dose, do not take an extra dose. Just resume your usual schedule.
- Continue to follow a cholesterol-lowering diet while taking VYTORIN. Ask your doctor if you need diet information.
- Keep taking VYTORIN unless your doctor tells you to stop. If you stop taking VYTORIN, your cholesterol may rise again.

What should I do in case of an overdose?

Contact your doctor immediately.

What are the possible side effects of VYTORIN?

See your doctor regularly to check your cholesterol level and to check for side effects. Your doctor may do blood tests to check your liver before you start taking VYTORIN and during treatment.

In clinical studies patients reported the following common side effects while taking VYTORIN: headache and muscle pain (see What should I tell my doctor before and while taking VYTORIN?).

The following side effects have been reported in general use with either ezetimibe or simvastatin tablets (tablets that contain the active ingredients of VYTORIN):

- allergic reactions including swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing or swallowing (which may require treatment right away), and rash; alterations in some laboratory blood tests; liver problems; inflammation of the pancreas; nausea; gallstones; inflammation of the gallbladder.

Tell your doctor if you are having these or any other medical problems while on VYTORIN. This is not a complete list of side effects. For a complete list, ask your doctor or pharmacist.

What should I know about high cholesterol?

Cholesterol is a type of fat found in your blood. Cholesterol comes from two sources. It is produced by your body and it comes from the food you eat. Your total cholesterol is made up of both LDL and HDL cholesterol.

LDL cholesterol is called "bad" cholesterol because it can build up in the wall of your arteries and form plaque. Over time, plaque build-up can cause a narrowing of the arteries. This narrowing can slow or block blood flow to your heart, brain, and other organs. High LDL cholesterol is a major cause of heart disease and stroke.

HDL cholesterol is called "good" cholesterol because it keeps the bad cholesterol from building up in the arteries.

Triglycerides also are fats found in your body.

General Information about VYTORIN

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use VYTORIN for a condition for which it was not prescribed. Do not give VYTORIN to other people, even if they have the same condition you have. It may harm them.

This summarizes the most important information about VYTORIN. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about VYTORIN that is written for health professionals. For additional information, visit the following web site: vytorin.com.

Inactive ingredients:

Butylated hydroxyanisole NF, citric acid monohydrate USP, croscarmellose sodium NF, hydroxypropyl methylcellulose USP, lactose monohydrate NF, magnesium stearate NF, microcrystalline cellulose NF, and propyl gallate NF.

9621002 Issued November 2004

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Merck/Schering-Plough Pharmaceuticals
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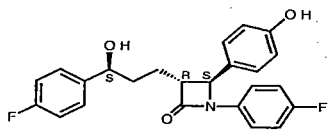
Shown in Product Identification Guide, page 323

ZETIA® ℞

[zĕt′ ē ă]
(ezetimibe)
TABLETS

DESCRIPTION

ZETIA (ezetimibe) is in a class of lipid-lowering compounds that selectively inhibits the intestinal absorption of cholesterol and related phytosterols. The chemical name of ezetimibe is 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone. The empirical formula is $C_{24}H_{21}F_2NO_3$. Its molecular weight is 409.4 and its structural formula is:



Ezetimibe is a white, crystalline powder that is freely to very soluble in ethanol, methanol, and acetone and practically insoluble in water. Ezetimibe has a melting point of about 163°C and is stable at ambient temperature. ZETIA is available as a tablet for oral administration containing 10 mg of ezetimibe and the following inactive ingredients: croscarmellose sodium NF, lactose monohydrate NF, magnesium stearate NF, microcrystalline cellulose NF, povidone USP, and sodium lauryl sulfate NF.

CLINICAL PHARMACOLOGY

Background

Clinical studies have demonstrated that elevated levels of total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C) and apolipoprotein B (Apo B), the major protein constituent of LDL, promote human atherosclerosis. In addition, decreased levels of high density lipoprotein cholesterol (HDL-C) are associated with the development of atherosclerosis. Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

ZETIA reduces total-C, LDL-C, Apo B, and TG, and increases HDL-C in patients with hypercholesterolemia. Administration of ZETIA with an HMG-CoA reductase inhibitor is effective in improving serum total-C, LDL-C, Apo B, TG, and HDL-C beyond either treatment alone. The effects of ezetimibe given either alone or in addition to an HMG-CoA reductase inhibitor on cardiovascular morbidity and mortality have not been established.

Mode of Action

Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine. In a 2-week clinical study in 18 hypercholesterolemic patients, ZETIA inhibited intestinal cholesterol absorption by 54%, compared with placebo. ZETIA had no clinically meaningful effect on the plasma concentrations of the fat-soluble vitamins A, D, and E (in a study of 113 patients), and did not impair adrenocortical steroid hormone production (in a study of 118 patients).

The cholesterol content of the liver is derived predominantly from three sources. The liver can synthesize cholesterol, take up cholesterol from the blood from circulating lipoproteins, or take up cholesterol absorbed by the small intestine. Intestinal cholesterol is derived primarily from cholesterol secreted in the bile and from dietary cholesterol. Ezetimibe has a mechanism of action that differs from those of other classes of cholesterol-reducing compounds (HMG-CoA reductase inhibitors, bile acid sequestrants [resins], fibric acid derivatives, and plant stanols).

Ezetimibe does not inhibit cholesterol synthesis in the liver, or increase bile acid excretion. Instead, ezetimibe localizes and appears to act at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood; this distinct mechanism is complementary to that of HMG-CoA reductase inhibitors (see CLINICAL STUDIES).

Pharmacokinetics

Absorption

After oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). After a single 10-mg dose of ZETIA to fasted adults, mean ezetimibe peak plasma concentrations (C_{max}) of 3.4 to 5.5 ng/mL were attained within 4 to 12 hours (T_{max}). Ezetimibe-glucuronide mean C_{max} values of 45 to 71 ng/mL were achieved between 1 and 2 hours (T_{max}). There was no substantial deviation from dose proportionality between 5 and 20 mg. The absolute bioavailability of ezetimibe cannot be determined, as the compound is virtually insoluble in aqueous media suitable for injection. Ezetimibe has variable bioavailability; the coefficient of variation, based on inter-subject variability, was 35 to 60% for AUC values.

Effect of Food on Oral Absorption

Concomitant food administration (high fat or non-fat meals) had no effect on the extent of absorption of ezetimibe when administered as ZETIA 10-mg tablets. The C_{max} value of ezetimibe was increased by 38% with consumption of high fat meals. ZETIA can be administered with or without food.

Distribution

Ezetimibe and ezetimibe-glucuronide are highly bound (>90%) to human plasma proteins.

Metabolism and Excretion

Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary and renal excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all species evaluated.

In humans, ezetimibe is rapidly metabolized to ezetimibe-glucuronide. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20% and 80 to 90% of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with a half-life of approximately 22 hours for both ezetimibe and ezetimibe-glucuronide. Plasma concentration-time profiles exhibit multiple peaks, suggesting enterohepatic recycling. Following oral administration of ^{14}C-ezetimibe (20 mg) to human subjects, total ezetimibe (ezetimibe + ezetimibe-glucuronide) accounted for approximately 93% of the total radioactivity in plasma. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Approximately 78% and 11% of the administered radioactivity were recovered in the feces and urine, respectively, over a 10-day collection period. Ezetimibe was the major component in feces and accounted for 69% of the administered dose, while ezetimibe-glucuronide was the major component in urine and accounted for 9% of the administered dose.

Special Populations

Geriatric Patients

In a multiple dose study with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were about 2-fold higher in older (≥65 years) healthy subjects compared to younger subjects.

Pediatric Patients

In a multiple dose study with ezetimibe given 10 mg once daily for 7 days, the absorption and metabolism of ezetimibe were similar in adolescents (10 to 18 years) and adults. Based on total ezetimibe, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the pediatric population <10 years of age are not available.

Gender

In a multiple dose study with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were slightly higher (<20%) in women than in men.

Race

Based on a meta-analysis of multiple-dose pharmacokinetic studies, there were no pharmacokinetic differences between Blacks and Caucasians. There were too few patients in other racial or ethnic groups to permit further pharmacokinetic comparisons.

Hepatic Insufficiency

After a single 10-mg dose of ezetimibe, the mean area under the curve (AUC) for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic insufficiency (Child-Pugh score 5 to 6), compared to healthy subjects. The mean AUC values for total ezetimibe and ezetimibe were increased approximately 3- to 4-fold and 5- to 6-fold, respectively, in patients with moderate (Child-Pugh score 7 to 9) or severe hepatic impairment (Child-Pugh score 10 to 15). In a 14-day, multiple-dose study (10 mg daily) in patients with

moderate hepatic insufficiency, the mean AUC values for total ezetimibe and ezetimibe were increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ZETIA is not recommended in these patients (see CONTRAINDICATIONS and PRECAUTIONS, *Hepatic Insufficiency*).

Renal Insufficiency

After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl ≤30 mL/min/1.73 m^2), the mean AUC values for total ezetimibe, ezetimibe-glucuronide, and ezetimibe were increased approximately 1.5-fold, compared to healthy subjects (n=9).

Drug Interactions(See also PRECAUTIONS, *Drug Interactions*)

ZETIA had no significant effect on a series of probe drugs (caffeine, dextromethorphan, tolbutamide, and IV midazolam) known to be metabolized by cytochrome P450 (1A2, 2D6, 2C8/9 and 3A4) in a "cocktail" study of twelve healthy adult males. This indicates that ezetimibe is neither an inhibitor nor an inducer of these cytochrome P450 isozymes, and it is unlikely that ezetimibe will affect the metabolism of drugs that are metabolized by these enzymes.

Warfarin: Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males. There have been post-marketing reports of increased International Normalized Ratio (INR) in patients who had ezetimibe added to warfarin. Most of these patients were also on other medications (See PRECAUTIONS, *Drug Interactions*).

Digoxin: Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on the bioavailability of digoxin and the ECG parameters (HR, PR, QT, and QTc intervals) in a study of twelve healthy adult males.

Gemfibrozil: In a study of twelve healthy adult males, concomitant administration of gemfibrozil (600 mg twice daily) significantly increased the oral bioavailability of total ezetimibe by a factor of 1.7. Ezetimibe (10 mg once daily) did not significantly affect the bioavailability of gemfibrozil.

Oral Contraceptives: Co-administration of ezetimibe (10 mg once daily) with oral contraceptives had no significant effect on the bioavailability of ethinyl estradiol or levonorgestrel in a study of eighteen healthy adult females.

Cimetidine: Multiple doses of cimetidine (400 mg twice daily) had no significant effect on the oral bioavailability of ezetimibe and total ezetimibe in a study of twelve healthy adults.

Antacids: In a study of twelve healthy adults, a single dose of antacid (Supralox™ 20 mL) administration had no significant effect on the oral bioavailability of total ezetimibe, ezetimibe-glucuronide, or ezetimibe based on AUC values. The C_{max} value of total ezetimibe was decreased by 30%.

Glipizide: In a study of twelve healthy adult males, steady-state levels of ezetimibe (10 mg once daily) had no significant effect on the pharmacokinetics and pharmacodynamics of glipizide. A single dose of glipizide (10 mg) had no significant effect on the exposure to total ezetimibe or ezetimibe.

HMG-CoA Reductase Inhibitors: In studies of healthy hypercholesterolemic (LDL-C ≥130 mg/dL) adult subjects, concomitant administration of ezetimibe (10 mg once daily) had no significant effect on the bioavailability of either lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin, or rosuvastatin. No significant effect on the bioavailability of total ezetimibe and ezetimibe was demonstrated by either lovastatin (20 mg once daily), pravastatin (20 mg once daily), atorvastatin (10 mg once daily), fluvastatin (20 mg once daily), or rosuvastatin (10 mg once daily). (See PRECAUTIONS, *Skeletal Muscle*).

Fenofibrate: In a study of thirty-two healthy hypercholesterolemic (LDL-C ≥130 mg/dL) adult subjects, concomitant fenofibrate (200 mg once daily) administration increased the mean C_{max} and AUC values of total ezetimibe approximately 64% and 48%, respectively. Pharmacokinetics of fenofibrate were not significantly affected by ezetimibe (10 mg once daily).

Cholestyramine: In a study of forty healthy hypercholesterolemic (LDL-C ≥130 mg/dL) adult subjects, concomitant cholestyramine (4 g twice daily) administration decreased the mean AUC values of total ezetimibe and ezetimibe approximately 55% and 80%, respectively.

Cyclosporine: In a study of eight post-renal transplant patients with mildly impaired or normal renal function (creatinine clearance of >50 mL/min), stable doses of cyclosporine (75 to 150 mg twice daily) increased the mean AUC and C_{max} values of total ezetimibe 3.4-fold (range 2.3- to 7.9-fold) and 3.9-fold (range 3.0- to 4.4-fold), respectively, compared to a historical healthy control population (n=17). In a different study, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13.2 mL/min/1.73 m^2) who was receiving multiple medications, including cyclosporine, demonstrated a 12-fold greater exposure to total ezetimibe compared to healthy subjects. In a two-period crossover study in twelve healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100-mg dose of cyclosporine on Day 7 resulted in a mean 15% increase in cyclosporine AUC (range 10% decrease to 51% increase) compared to a single 100-mg dose of cyclosporine alone (see PRECAUTIONS, *Drug Interactions*).

ANIMAL PHARMACOLOGY

The hypocholesterolemic effect of ezetimibe was evaluated in cholesterol-fed Rhesus monkeys, dogs, rats, and mouse models of human cholesterol metabolism. Ezetimibe was found to have an ED_{50} value of 0.5 µg/kg/day for inhibiting the rise in plasma cholesterol levels in monkeys. The ED_{50} values in dogs, rats, and mice were 7, 30, and 700 µg/kg/day, respectively. These results are consistent with ZETIA being a potent cholesterol absorption inhibitor.

In a rat model, where the glucuronide metabolite of ezetimibe (SCH 60663) was administered intraduodenally, the metabolite was as potent as the parent compound (SCH 58235) in inhibiting the absorption of cholesterol, suggesting that the glucuronide metabolite had activity similar to the parent drug.

In 1-month studies in dogs given ezetimibe (0.03 to 300 mg/kg/day), the concentration of cholesterol in gallbladder bile increased ~2- to 4-fold. However, a dose of 300 mg/kg/day administered to dogs for one year did not result in gallstone formation or any other adverse hepatobiliary effects. In a 14-day study in mice given ezetimibe (0.3-5 mg/kg/day) and fed a low-fat or cholesterol-rich diet, the concentration of cholesterol in gallbladder bile was either unaffected or reduced to normal levels, respectively.

A series of acute preclinical studies was performed to determine the selectivity of ZETIA for inhibiting cholesterol absorption. Ezetimibe inhibited the absorption of ^{14}C-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethyl estradiol, or the fat-soluble vitamins A and D.

Table 1
Response to ZETIA in Patients with Primary Hypercholesterolemia
(Mean[a] % Change from Untreated Baseline[b])

	Treatment group	N	Total-C	LDL-C	Apo B	TG[a]	HDL-C
Study 1[c]	Placebo	205	+1	+1	-1	-1	-1
	Ezetimibe	622	-12	-18	-15	-7	+1
Study 2[c]	Placebo	226	+1	+1	-1	+2	-2
	Ezetimibe	666	-12	-18	-16	-9	+1
Pooled Data[c] (Studies 1 & 2)	Placebo	431	0	+1	-2	0	-2
	Ezetimibe	1288	-13	-18	-16	-8	+1

[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] ZETIA significantly reduced total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to placebo.

Table 2
Response to Addition of ZETIA to On-going HMG-CoA Reductase Inhibitor Therapy[a] in Patients with Hypercholesterolemia
(Mean[b] % Change from Treated Baseline[c])

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG[b]	HDL-C
On-going HMG-CoA reductase inhibitor +Placebo[d]	390	-2	-4	-3	-3	+1
On-going HMG-CoA reductase inhibitor +ZETIA[d]	379	-17	-25	-19	-14	+3

[a] Patients receiving each HMG-CoA reductase inhibitor: 40% atorvastatin, 31% simvastatin, 29% others (pravastatin, fluvastatin, cerivastatin, lovastatin)
[b] For triglycerides, median % change from baseline
[c] Baseline - on an HMG-CoA reductase inhibitor alone.
[d] ZETIA + HMG-CoA reductase inhibitor significantly reduced total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to HMG-CoA reductase inhibitor alone.

Table 3
Response to ZETIA and Atorvastatin Initiated Concurrently in Patients with Primary Hypercholesterolemia
(Mean[a] % Change from Untreated Baseline[b])

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG[a]	HDL-C
Placebo	60	+4	+4	+3	-6	+4
ZETIA	65	-14	-20	-15	-5	+4
Atorvastatin 10 mg	60	-26	-37	-28	-21	+6
ZETIA + Atorvastatin 10 mg	65	-38	-53	-43	-31	+9
Atorvastatin 20 mg	60	-30	-42	-34	-23	+4
ZETIA + Atorvastatin 20 mg	62	-39	-54	-44	-30	+9
Atorvastatin 40 mg	66	-32	-45	-37	-24	+4
ZETIA + Atorvastatin 40 mg	65	-42	-56	-45	-34	+5
Atorvastatin 80 mg	62	-40	-54	-46	-31	+3
ZETIA + Atorvastatin 80 mg	63	-46	-61	-50	-40	+7
Pooled data (All Atorvastatin Doses)[c]	248	-32	-44	-36	-24	+4
Pooled data (All ZETIA + Atorvastatin Doses)[c]	255	-41	-56	-45	-33	+7

[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] ZETIA + all doses of atorvastatin pooled (10-80 mg) significantly reduced total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to all doses of atorvastatin pooled (10-80 mg).

Continued on next page

Zetia—Cont.

In 4- to 12-week toxicity studies in mice, ezetimibe did not induce cytochrome P450 drug metabolizing enzymes. In toxicity studies, a pharmacokinetic interaction of ezetimibe with HMG-CoA reductase inhibitors (parents or their active hydroxy acid metabolites) was seen in rats, dogs, and rabbits.

CLINICAL STUDIES

Primary Hypercholesterolemia

ZETIA reduces total-C, LDL-C, Apo B, and TG, and increases HDL-C in patients with hypercholesterolemia. Maximal to near maximal response is generally achieved within 2 weeks and maintained during chronic therapy.

ZETIA is effective in patients with hypercholesterolemia, in men and women, in younger and older patients, alone or administered with an HMG-CoA reductase inhibitor. Experience in pediatric and adolescent patients (ages 9 to 17) has been limited to patients with homozygous familial hypercholesterolemia (HoFH) or sitosterolemia.

Experience in non-Caucasians is limited and does not permit a precise estimate of the magnitude of the effects of ZETIA.

Monotherapy

In two, multicenter, double-blind, placebo-controlled, 12-week studies in 1719 patients with primary hypercholesterolemia, ZETIA significantly lowered total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to placebo (see Table 1). Reduction in LDL-C was consistent across age, sex, and baseline LDL-C.

[See table 1 at top of previous page]

Combination with HMG-CoA Reductase Inhibitors

ZETIA Added to On-going HMG-CoA Reductase Inhibitor Therapy

In a multicenter, double-blind, placebo-controlled, 8-week study, 769 patients with primary hypercholesterolemia, known coronary heart disease or multiple cardiovascular risk factors who were already receiving HMG-CoA reductase inhibitor monotherapy, but who had not met their NCEP ATP II target LDL-C goal were randomized to receive either ZETIA or placebo in addition to their on-going HMG-CoA reductase inhibitor therapy.

ZETIA, added to on-going HMG-CoA reductase inhibitor therapy, significantly lowered total-C, LDL-C, Apo B, and TG, and increased HDL-C compared with an HMG-CoA reductase inhibitor administered alone (see Table 2). LDL-C reductions induced by ZETIA were generally consistent across all HMG-CoA reductase inhibitors.

[See table 2 at top of previous page]

ZETIA Initiated Concurrently with an HMG-CoA Reductase Inhibitor

In four, multicenter, double-blind, placebo-controlled, 12-week trials, in 2382 hypercholesterolemic patients, ZETIA or placebo was administered alone or with various doses of atorvastatin, simvastatin, pravastatin, or lovastatin.

When all patients receiving ZETIA with an HMG-CoA reductase inhibitor were compared to all those receiving the corresponding HMG-CoA reductase inhibitor alone, ZETIA significantly lowered total-C, LDL-C, Apo B, and TG, and, with the exception of pravastatin, increased HDL-C compared to the HMG-CoA reductase inhibitor administered alone. LDL-C reductions induced by ZETIA were generally consistent across all HMG-CoA reductase inhibitors. (See footnote c, Tables 3 to 6.)

[See table 3 on previous page]
[See table 4 above]
[See table 5 at right]
[See table 6 at top of next page]

Homozygous Familial Hypercholesterolemia (HoFH)

A study was conducted to assess the efficacy of ZETIA in the treatment of HoFH. This double-blind, randomized, 12-week study enrolled 50 patients with a clinical and/or genotypic diagnosis of HoFH, with or without concomitant LDL apheresis, already receiving atorvastatin or simvastatin (40 mg). Patients were randomized to one of three treatment groups, atorvastatin or simvastatin (80 mg), ZETIA administered with atorvastatin or simvastatin (40 mg), or ZETIA administered with atorvastatin or simvastatin (80 mg). Due to decreased bioavailability of ezetimibe in patients concomitantly receiving cholestyramine (see PRECAUTIONS), ezetimibe was dosed at least 4 hours before or after administration of resins. Mean baseline LDL-C was 341 mg/dL in those patients randomized to atorvastatin 80 mg or simvastatin 80 mg alone and 316 mg/dL in the group randomized to ZETIA plus atorvastatin 40 or 80 mg or simvastatin 40 or 80 mg. ZETIA, administered with atorvastatin or simvastatin (40 and 80 mg statin groups, pooled), significantly reduced LDL-C (21%) compared with increasing the dose of simvastatin or atorvastatin monotherapy from 40 to 80 mg (7%). In those treated with ZETIA plus 80 mg atorvastatin or with ZETIA plus 80 mg simvastatin, LDL-C was reduced by 27%.

Homozygous Sitosterolemia (Phytosterolemia)

A study was conducted to assess the efficacy of ZETIA in the treatment of homozygous sitosterolemia. In this multicenter, double-blind, placebo-controlled, 8-week trial, 37 patients with homozygous sitosterolemia with elevated plasma sitosterol levels (>5 mg/dL) on their current therapeutic regimen (diet, bile-acid-binding resins, HMG-CoA reductase inhibitors, ileal bypass surgery and/or LDL apheresis), were randomized to receive ZETIA (n=30) or placebo (n=7). Due to decreased bioavailability of ezetimibe in patients concomitantly receiving cholestyramine (see PRECAUTIONS), ezetimibe was dosed at least 2 hours before or 4 hours after resins were administered. Excluding the one subject receiving LDL apheresis, ZETIA significantly lowered plasma sitosterol and campesterol, by 21% and 24% from baseline, respectively. In contrast, patients who received placebo had increases in sitosterol and campesterol of 4% and 3% from baseline, respectively. For patients treated with ZETIA, mean plasma levels of plant sterols were reduced progressively over the course of the study. The effects of reducing plasma sitosterol and campesterol on reducing the risks of cardiovascular morbidity and mortality have not been established.

Reductions in sitosterol and campesterol were consistent between patients taking ZETIA concomitantly with bile acid sequestrants (n=8) and patients not on concomitant bile acid sequestrant therapy (n=21).

Table 4
Response to ZETIA and Simvastatin Initiated Concurrently in Patients with Primary Hypercholesterolemia (Mean[a] % Change from Untreated Baseline[b])

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG[a]	HDL-C
Placebo	70	-1	-1	0	+2	+1
ZETIA	61	-13	-19	-14	-11	+5
Simvastatin 10 mg	70	-18	-27	-21	-14	+8
ZETIA + Simvastatin 10 mg	67	-32	-46	-35	-26	+9
Simvastatin 20 mg	61	-26	-36	-29	-18	+6
ZETIA + Simvastatin 20 mg	69	-33	-46	-36	-25	+9
Simvastatin 40 mg	65	-27	-38	-32	-24	+6
ZETIA + Simvastatin 40 mg	73	-40	-56	-45	-32	+11
Simvastatin 80 mg	67	-32	-45	-37	-23	+8
ZETIA + Simvastatin 80 mg	65	-41	-58	-47	-31	+8
Pooled data (All Simvastatin Doses)[c]	263	-26	-36	-30	-20	+7
Pooled data (All ZETIA + Simvastatin Doses)[c]	274	-37	-51	-41	-29	+9

[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] ZETIA + all doses of simvastatin pooled (10-80 mg) significantly reduced total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to all doses of simvastatin pooled (10-80 mg).

Table 5
Response to ZETIA and Pravastatin Initiated Concurrently in Patients with Primary Hypercholesterolemia (Mean[a] % Change from Untreated Baseline[b])

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG[a]	HDL-C
Placebo	65	0	-1	-2	-1	+2
ZETIA	64	-13	-20	-15	-5	+4
Pravastatin 10 mg	66	-15	-21	-16	-14	+6
ZETIA + Pravastatin 10 mg	71	-24	-34	-27	-23	+8
Pravastatin 20 mg	69	-15	-23	-18	-8	+8
ZETIA + Pravastatin 20 mg	66	-27	-40	-31	-21	+8
Pravastatin 40 mg	70	-22	-31	-26	-19	+6
ZETIA + Pravastatin 40 mg	67	-30	-42	-32	-21	+8
Pooled data (All Pravastatin Doses)[c]	205	-17	-25	-20	-14	+7
Pooled data (All ZETIA + Pravastatin Doses)[c]	204	-27	-39	-30	-21	+8

[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] ZETIA + all doses of pravastatin pooled (10-40 mg) significantly reduced total-C, LDL-C, Apo B, and TG compared to all doses of pravastatin pooled (10-40 mg).

INDICATIONS AND USAGE

Primary Hypercholesterolemia

Monotherapy

ZETIA, administered alone, is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, and Apo B in patients with primary (heterozygous familial and non-familial) hypercholesterolemia.

Combination Therapy with HMG-CoA Reductase Inhibitors

ZETIA, administered in combination with an HMG-CoA reductase inhibitor, is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, and Apo B in patients with primary (heterozygous familial and non-familial) hypercholesterolemia.

Homozygous Familial Hypercholesterolemia (HoFH)

The combination of ZETIA and atorvastatin or simvastatin is indicated for the reduction of elevated total-C and LDL-C levels in patients with HoFH, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

Homozygous Sitosterolemia

ZETIA is indicated as adjunctive therapy to diet for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia.

Therapy with lipid-altering agents should be a component of multiple risk-factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid-altering agents should be used in addition

to an appropriate diet (including restriction of saturated fat and cholesterol) and when the response to diet and other non-pharmacological measures has been inadequate. (See NCEP Adult Treatment Panel (ATP) III Guidelines, summarized in Table 7.)

[See table 7 below]

Prior to initiating therapy with ZETIA, secondary causes for dyslipidemia (i.e., diabetes, hypothyroidism, obstructive liver disease, chronic renal failure, and drugs that increase LDL-C and decrease HDL-C [progestins, anabolic steroids, and corticosteroids]), should be excluded or, if appropriate, treated. A lipid profile should be performed to measure total-C, LDL-C, HDL-C and TG. For TG levels >400 mg/dL (>4.5 mmol/L), LDL-C concentrations should be determined by ultracentrifugation.

At the time of hospitalization for an acute coronary event, lipid measures should be taken on admission or within 24 hours. These values can guide the physician on initiation of LDL-lowering therapy before or at discharge.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

The combination of ZETIA with an HMG-CoA reductase inhibitor is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.

All HMG-CoA reductase inhibitors are contraindicated in pregnant and nursing women. When ZETIA is administered with an HMG-CoA reductase inhibitor in a woman of childbearing potential, refer to the pregnancy category and product labeling for the HMG-CoA reductase inhibitor. (See PRECAUTIONS, *Pregnancy*.)

PRECAUTIONS

Concurrent administration of ZETIA with a specific HMG-CoA reductase inhibitor should be in accordance with the product labeling for that HMG-CoA reductase inhibitor.

Liver Enzymes

In controlled clinical monotherapy studies, the incidence of consecutive elevations (≥3 × the upper limit of normal [ULN]) in serum transaminases was similar between ZETIA (0.5%) and placebo (0.3%).

In controlled clinical combination studies of ZETIA initiated concurrently with an HMG-CoA reductase inhibitor, the incidence of consecutive elevations (≥3 × ULN) in serum transaminases was 1.3% for patients treated with ZETIA administered with HMG-CoA reductase inhibitors and 0.4% for patients treated with HMG-CoA reductase inhibitors alone. These elevations in transaminases were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment. When ZETIA is co-administered with an HMG-CoA reductase inhibitor, liver function tests should be performed at initiation of therapy and according to the recommendations of the HMG-CoA reductase inhibitor.

Skeletal Muscle

In clinical trials, there was no excess of myopathy or rhabdomyolysis associated with ZETIA compared with the relevant control arm (placebo or HMG-CoA reductase inhibitor alone). However, myopathy and rhabdomyolysis are known adverse reactions to HMG-CoA reductase inhibitors and other lipid-lowering drugs. In clinical trials, the incidence of CPK >10 X ULN was 0.2% for ZETIA vs 0.1% for placebo, and 0.1% for ZETIA co-administered with an HMG-CoA reductase inhibitor vs 0.4% for HMG-CoA reductase inhibitors alone.

In post-marketing experience with ZETIA, cases of myopathy and rhabdomyolysis have been reported regardless of causality. Most patients who developed rhabdomyolysis were taking an HMG-CoA reductase inhibitor prior to initiating ZETIA. However, rhabdomyolysis has been reported very rarely with ZETIA monotherapy and very rarely with the addition of ZETIA to agents known to be associated with increased risk of rhabdomyolysis, such as fibrates. All patients starting therapy with ezetimibe should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. ZETIA and any HMG-CoA reductase inhibitor or fibrate that the patient is taking concomitantly should be immediately discontinued if myopathy is diagnosed or suspected. The presence of these symptoms and a creatine phosphokinase (CPK) level >10 times the ULN indicates myopathy.

Hepatic Insufficiency

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ZETIA is not recommended in these patients. (See CLINICAL PHARMACOLOGY, *Special Populations*.)

Drug Interactions (See also CLINICAL PHARMACOLOGY, *Drug Interactions*)

Cholestyramine: Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe approximately 55%. The incremental LDL-C reduction due to adding ezetimibe to cholestyramine may be reduced by this interaction.

Fibrates: The safety and effectiveness of ezetimibe administered with fibrates have not been established.

Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile (see ANIMAL PHARMACOLOGY). Co-administration of ZETIA with fibrates is not recommended until use in patients is studied.

Table 6
Response to ZETIA and Lovastatin Initiated Concurrently in Patients with Primary Hypercholesterolemia (Mean[a] % Change from Untreated Baseline[b])

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG[a]	HDL-C
Placebo	64	+1	0	+1	+6	0
ZETIA	72	-13	-19	-14	-5	+3
Lovastatin 10 mg	73	-15	-20	-17	-11	+5
ZETIA + Lovastatin 10 mg	65	-24	-34	-27	-19	+8
Lovastatin 20 mg	74	-19	-26	-21	-12	+3
ZETIA + Lovastatin 20 mg	62	-29	-41	-34	-27	+9
Lovastatin 40 mg	73	-21	-30	-25	-15	+5
ZETIA + Lovastatin 40 mg	65	-33	-46	-38	-27	+9
Pooled data (All Lovastatin Doses)[c]	220	-18	-25	-21	-12	+4
Pooled data (All ZETIA + Lovastatin Doses)[c]	192	-29	-40	-33	-25	+9

[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] ZETIA + all doses of lovastatin pooled (10-40 mg) significantly reduced total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to all doses of lovastatin pooled (10-40 mg).

Table 7
Summary of NCEP ATP III Guidelines

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes[a] (mg/dL)	LDL level at Which to Consider Drug Therapy (mg/dL)
CHD or CHD risk equivalents[b] (10-year risk >20%)[c]	<100	≥100	≥130 (100-129: drug optional)[d]
2+ Risk factors[e] (10-year risk ≤20%)[c]	<130	≥130	10-year risk 10-20%: ≥130[c] 10-year risk <10%: ≥160[c]
0-1 Risk factor[f]	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

[a] Therapeutic lifestyle changes include: 1) dietary changes: reduced intake of saturated fats (<7% of total calories) and cholesterol (<200 mg per day), and enhancing LDL lowering with plant stanols/sterols (2 g/d) and increased viscous (soluble) fiber (10-25 g/d), 2) weight reduction, and 3) increased physical activity.
[b] CHD risk equivalents comprise: diabetes, multiple risk factors that confer a 10-year risk for CHD >20%, and other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm and symptomatic carotid artery disease).
[c] Risk assessment for determining the 10-year risk for developing CHD is carried out using the Framingham risk scoring. Refer to JAMA, May 16, 2001; 285 (19): 2486-2497, or the NCEP website (http://www.nhlbi.nih.gov) for more details.
[d] Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.
[e] Major risk factors (exclusive of LDL cholesterol) that modify LDL goals include cigarette smoking, hypertension (BP ≥140/90 mm Hg or on anti-hypertensive medication), low HDL cholesterol (<40 mg/dL), family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years), age (men ≥45 years; women ≥55 years). HDL cholesterol ≥60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count.
[f] Almost all people with 0-1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

Fenofibrate: In a pharmacokinetic study, concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold.

Gemfibrozil: In a pharmacokinetic study, concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1.7-fold.

HMG-CoA Reductase Inhibitors: No clinically significant pharmacokinetic interactions were seen when ezetimibe was co-administered with atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, or rosuvastatin.

Cyclosporine: Caution should be exercised when using ZETIA and cyclosporine concomitantly due to increased exposure to both ezetimibe and cyclosporine. Cyclosporine concentrations should be monitored in patients receiving ZETIA and cyclosporine.

The degree of increase in ezetimibe exposure may be greater in patients with severe renal insufficiency. In patients treated with cyclosporine, the potential effects of the increased exposure to ezetimibe from concomitant use should be carefully weighed against the benefits of alterations in lipid levels provided by ezetimibe. In a pharmacokinetic study in post-renal transplant patients with mildly impaired or normal renal function (creatinine clearance of >50 mL/min), concomitant cyclosporine administration increased the mean AUC and C_{max} of total ezetimibe 3.4-fold (range 2.3- to 7.9-fold) and 3.9-fold (range 3.0- to 4.4-fold), respectively. In a separate study, the total ezetimibe exposure increased 12-fold in one renal transplant patient with severe renal insufficiency receiving multiple medications, including cyclosporine (see CLINICAL PHARMACOLOGY, *Drug Interactions*).

Warfarin: If ezetimibe is added to warfarin, the International Normalized Ratio should be appropriately monitored.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 104-week dietary carcinogenicity study with ezetimibe was conducted in rats at doses up to 1500 mg/kg/day (males) and 500 mg/kg/day (females) (~20 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe). A 104-week dietary carcinogenicity study with ezetimibe was also conducted in mice at doses up to 500 mg/kg/day (>150 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe). There were no statistically significant increases in tumor incidences in drug-treated rats or mice.

No evidence of mutagenicity was observed *in vitro* in a microbial mutagenicity (Ames) test with *Salmonella typhimurium* and *Escherichia coli* with or without metabolic activation. No evidence of clastogenicity was observed *in vitro* in a chromosomal aberration assay in human peripheral blood lymphocytes with or without metabolic activation. In addition, there was no evidence of genotoxicity in the *in vivo* mouse micronucleus test.

In oral (gavage) fertility studies of ezetimibe conducted in rats, there was no evidence of reproductive toxicity at doses

Continued on next page

Zetia—Cont.

up to 1000 mg/kg/day in male or female rats (~7 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe).

Pregnancy

Pregnancy Category: C

There are no adequate and well-controlled studies of ezetimibe in pregnant women. Ezetimibe should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

In oral (gavage) embryo-fetal development studies of ezetimibe conducted in rats and rabbits during organogenesis, there was no evidence of embryolethal effects at the doses tested (250, 500, 1000 mg/kg/day). In rats, increased incidences of common fetal skeletal findings (extra pair of thoracic ribs, unossified cervical vertebral centra, shortened ribs) were observed at 1000 mg/kg/day (~10 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe). In rabbits treated with ezetimibe, an increased incidence of extra thoracic ribs was observed at 1000 mg/kg/day (150 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe). Ezetimibe crossed the placenta when pregnant rats and rabbits were given multiple oral doses.

Multiple-dose studies of ezetimibe given in combination with HMG-CoA reductase inhibitors (statins) in rats and rabbits during organogenesis result in higher ezetimibe and statin exposures. Reproductive findings occur at lower doses in combination therapy compared to monotherapy.

All HMG-CoA reductase inhibitors are contraindicated in pregnant and nursing women. When ZETIA is administered with an HMG-CoA reductase inhibitor in a woman of childbearing potential, refer to the pregnancy category and product labeling for the HMG-CoA reductase inhibitor. (See CONTRAINDICATIONS.)

Labor and Delivery

The effects of ZETIA on labor and delivery in pregnant women are unknown.

Nursing Mothers

In rat studies, exposure to total ezetimibe in nursing pups was up to half of that observed in maternal plasma. It is not known whether ezetimibe is excreted into human breast milk; therefore, ZETIA should not be used in nursing mothers unless the potential benefit justifies the potential risk to the infant.

Pediatric Use

The pharmacokinetics of ZETIA in adolescents (10 to 18 years) have been shown to be similar to that in adults. Treatment experience with ZETIA in the pediatric population is limited to 4 patients (9 to 17 years) in the sitosterolemia study and 5 patients (11 to 17 years) in the HoFH study. Treatment with ZETIA in children (<10 years) is not recommended. (See CLINICAL PHARMACOLOGY, *Special Populations*.)

Geriatric Use

Of the patients who received ZETIA in clinical studies, 948 were 65 and older (this included 206 who were 75 and older). The effectiveness and safety of ZETIA were similar between these patients and younger subjects. Greater sensitivity of some older individuals cannot be ruled out. (See CLINICAL PHARMACOLOGY, *Special Populations*, and ADVERSE REACTIONS.)

ADVERSE REACTIONS

ZETIA has been evaluated for safety in more than 4700 patients in clinical trials. Clinical studies of ZETIA (administered alone or with an HMG-CoA reductase inhibitor) demonstrated that ZETIA was generally well tolerated. The overall incidence of adverse events reported with ZETIA was similar to that reported with placebo, and the discontinuation rate due to adverse events was also similar for ZETIA and placebo.

Monotherapy

Adverse experiences reported in ≥2% of patients treated with ZETIA and at an incidence greater than placebo in placebo-controlled studies of ZETIA, regardless of causality assessment, are shown in Table 8.

Table 8*
Clinical Adverse Events Occurring in ≥2% of Patients Treated with ZETIA and at an Incidence Greater than Placebo, Regardless of Causality

Body System/Organ Class Adverse Event	Placebo (%) n = 795	ZETIA 10 mg (%) n = 1691
Body as a whole – general disorders		
Fatigue	1.8	2.2
Gastro-intestinal system disorders		
Abdominal pain	2.8	3.0
Diarrhea	3.0	3.7
Infection and infestations		
Infection viral	1.8	2.2
Pharyngitis	2.1	2.3
Sinusitis	2.8	3.6
Musculo-skeletal system disorders		
Arthralgia	3.4	3.8
Back pain	3.9	4.1
Respiratory system disorders		
Coughing	2.1	2.3

*Includes patients who received placebo or ZETIA alone reported in Table 9.

The frequency of less common adverse events was comparable between ZETIA and placebo.

Combination with an HMG-CoA Reductase Inhibitor

ZETIA has been evaluated for safety in combination studies in more than 2000 patients.

In general, adverse experiences were similar between ZETIA administered with HMG-CoA reductase inhibitors and HMG-CoA reductase inhibitors alone. However, the frequency of increased transaminases was slightly higher in patients receiving ZETIA administered with HMG-CoA reductase inhibitors than in patients treated with HMG-CoA reductase inhibitors alone. (See PRECAUTIONS, *Liver Enzymes*.)

Clinical adverse experiences reported in ≥2% of patients and at an incidence greater than placebo in four placebo-controlled trials where ZETIA was administered alone or initiated concurrently with various HMG-CoA reductase inhibitors, regardless of causality assessment, are shown in Table 9.

[See table 9 below]

Post-marketing Experience

The following adverse reactions have been reported in post-marketing experience, regardless of causality assessment: Hypersensitivity reactions, including angioedema, rash, and urticaria; arthralgia; myalgia; elevated creatine phosphokinase; myopathy/rhabdomyolysis (very rarely; see PRECAUTIONS, *Skeletal Muscle*); elevations in liver transaminases; hepatitis; thrombocytopenia; pancreatitis; nausea; cholelithiasis; cholecystitis.

OVERDOSAGE

In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, or 40 mg/day to 18 patients with primary hypercholesterolemia for up to 56 days, was generally well tolerated.

A few cases of overdosage with ZETIA have been reported; most have not been associated with adverse experiences. Reported adverse experiences have not been serious. In the event of an overdose, symptomatic and supportive measures should be employed.

Table 9*
Clinical Adverse Events occurring in ≥2% of Patients and at an Incidence Greater than Placebo, Regardless of Causality, in ZETIA/Statin Combination Studies

Body System/Organ Class Adverse Event	Placebo (%) n=259	ZETIA 10 mg (%) n=262	All Statins** (%) n=936	ZETIA + All Statins** (%) n=925
Body as a whole – general disorders				
Chest pain	1.2	3.4	2.0	1.8
Dizziness	1.2	2.7	1.4	1.8
Fatigue	1.9	1.9	1.4	2.8
Headache	5.4	8.0	7.3	6.3
Gastro-intestinal system disorders				
Abdominal pain	2.3	2.7	3.1	3.5
Diarrhea	1.5	3.4	2.9	2.8
Infection and infestations				
Pharyngitis	1.9	3.1	2.5	2.3
Sinusitis	1.9	4.6	3.6	3.5
Upper respiratory tract infection	10.8	13.0	13.6	11.8
Musculo-skeletal system disorders				
Arthralgia	2.3	3.8	4.3	3.4
Back pain	3.5	3.4	3.7	4.3
Myalgia	4.6	5.0	4.1	4.5

*Includes four placebo-controlled combination studies in which ZETIA was initiated concurrently with an HMG-CoA reductase inhibitor.

**All Statins = all doses of all HMG-CoA reductase inhibitors.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving ZETIA and should continue on this diet during treatment with ZETIA.

The recommended dose of ZETIA is 10 mg once daily. ZETIA can be administered with or without food.

ZETIA may be administered with an HMG-CoA reductase inhibitor for incremental effect. For convenience, the daily dose of ZETIA may be taken at the same time as the HMG-CoA reductase inhibitor, according to the dosing recommendations for the HMG-CoA reductase inhibitor.

Patients with Hepatic Insufficiency

No dosage adjustment is necessary in patients with mild hepatic insufficiency (see PRECAUTIONS, *Hepatic Insufficiency*).

Patients with Renal Insufficiency

No dosage adjustment is necessary in patients with renal insufficiency (see CLINICAL PHARMACOLOGY, *Special Populations*).

Geriatric Patients

No dosage adjustment is necessary in geriatric patients (see CLINICAL PHARMACOLOGY, *Special Populations*).

Co-administration with Bile Acid Sequestrants

Dosing of ZETIA should occur either ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant (see PRECAUTIONS, *Drug Interactions*).

HOW SUPPLIED

No. 3861 - Tablets ZETIA, 10 mg, are white to off-white, capsule-shaped tablets debossed with "414" on one side. They are supplied as follows:

NDC 66582-414-31 bottles of 30
NDC 66582-414-54 bottles of 90
NDC 66582-414-74 bottles of 500
NDC 66582-414-28 unit dose packages of 100.

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.] Protect from moisture.

29480907T
REV 08
Issued July 2005
Printed in USA.
Manufactured for:
Merck/Schering-Plough Pharmaceuticals
North Wales, PA 19454, USA
By:
Schering Corporation
Kenilworth, NJ 07033, USA
or
Merck & Co., Inc.
Whitehouse Station, NJ 08889, USA

ZETIA® (ezetimibe) Tablets

Patient Information about ZETIA (zĕt'-ē-ă)

Generic name: ezetimibe (ē-zĕt'-ĕ-mīb)

Read this information carefully before you start taking ZETIA and each time you get more ZETIA. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about ZETIA, ask your doctor. Only your doctor can determine if ZETIA is right for you.

What is ZETIA?

ZETIA is a medicine used to lower levels of total cholesterol and LDL (bad) cholesterol in the blood. It is used for patients who cannot control their cholesterol levels by diet alone. It can be used by itself or with other medicines to treat high cholesterol. You should stay on a cholesterol-lowering diet while taking this medicine.

ZETIA works to reduce the amount of cholesterol your body absorbs. ZETIA does not help you lose weight.

For more information about cholesterol, see the "What should I know about high cholesterol?" section that follows.

Who should not take ZETIA?

- Do not take ZETIA if you are allergic to ezetimibe, the active ingredient in ZETIA, or to the inactive ingredients. For a list of inactive ingredients, see the "Inactive ingredients" section that follows.
- If you have active liver disease, do not take ZETIA while taking cholesterol-lowering medicines called statins.
- If you are pregnant or breast-feeding, do not take ZETIA while taking a statin.

What should I tell my doctor before and while taking ZETIA?

Tell your doctor about any prescription and non-prescription medicines you are taking or plan to take, including natural or herbal remedies.

Tell your doctor about all your medical conditions including allergies.

Tell your doctor if you:

- ever had liver problems. ZETIA may not be right for you.
- are pregnant or plan to become pregnant. Your doctor will decide if ZETIA is right for you.
- are breast-feeding. We do not know if ZETIA can pass to your baby through your milk. Your doctor will decide if ZETIA is right for you.
- experience unexplained muscle pain, tenderness, or weakness.

How should I take ZETIA?

- Take ZETIA once a day, with or without food. It may be easier to remember to take your dose if you do it at the same time every day, such as with breakfast, dinner, or at

bedtime. If you also take another medicine to reduce your cholesterol, ask your doctor if you can take them at the same time.
- If you forget to take ZETIA, take it as soon as you remember. However, do not take more than one dose of ZETIA a day.
- Continue to follow a cholesterol-lowering diet while taking ZETIA. Ask your doctor if you need diet information.
- Keep taking ZETIA unless your doctor tells you to stop. It is important that you keep taking ZETIA even if you do not feel sick.

See your doctor regularly to check your cholesterol level and to check for side effects. Your doctor may do blood tests to check your liver before you start taking ZETIA with a statin and during treatment.

What are the possible side effects of ZETIA?

In clinical studies patients reported few side effects while taking ZETIA. These included stomach pain and feeling tired.

Very rarely, patients have experienced severe muscle problems while taking ZETIA, usually when ZETIA was added to a statin drug. If you experience unexplained muscle pain, tenderness, or weakness while taking ZETIA, contact your doctor immediately. You need to do this promptly, because on rare occasions, these mucle problems can be serious, with muscle breakdown resulting in kidney damage.

Additionally, the following side effects have been reported in general use: allergic reactions (which may require treatment right away) including swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing or swallowing, rash, and hives; joint pain; muscle aches; alterations in some laboratory blood tests; liver problems; inflammation of the pancreas; nausea; gallstones; inflammation of the gallbladder.

Tell your doctor if you are having these or any other medical problems while on ZETIA. For a complete list of side effects, ask your doctor or pharmacist.

What should I know about high cholesterol?

Cholesterol is a type of fat found in your blood. Your total cholesterol is made up of LDL and HDL cholesterol.

LDL cholesterol is called "bad" cholesterol because it can build up in the wall of your arteries and form plaque. Over time, plaque build-up can cause a narrowing of the arteries. This narrowing can slow or block blood flow to your heart, brain, and other organs. High LDL cholesterol is a major cause of heart disease and stroke.

HDL cholesterol is called "good" cholesterol because it keeps the bad cholesterol from building up in the arteries.

Triglycerides also are fats found in your blood.

General Information about ZETIA

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use ZETIA for a condition for which it was not prescribed. Do not give ZETIA to other people, even if they have the same condition you have. It may harm them.

This summarizes the most important information about ZETIA. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about ZETIA that is written for health professionals.

Inactive ingredients:

Croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate.

29480800T
Rev-08
Issued July 2005

Manufactured for:
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North Wales, PA 19454, USA
By:
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Kenilworth, NJ 07033, USA
or
Merck & Co., Inc.
Whitehouse Station, NJ 08889, USA

Shown in Product Identification Guide, page 323

NOTICE
Before prescribing or administering any product described in PHYSICIANS' DESK REFERENCE check the **PDR Supplements** for revised information.

Mericon Industries, Inc.
8819 N. PIONEER ROAD
PEORIA, IL 61615

Direct Inquiries to:
William R. Connelly
(309) 693-2150
FAX: (309) 693-2158

BIOTIN OTC
[*'bī-ō-tĭn*]
biotin supplement–high potency

ACTIVE INGREDIENTS
Biotin 5 mg

DIRECTIONS
Take one capsule daily or as directed by your physician.

HOW SUPPLIED
Biotin is supplied as capsules in bottles of 120.
NDC 00394-0130-12

FLORICAL® OTC
[*flor ĭ cal*]
(fluoride and calcium supplement)

ACTIVE INGREDIENTS
Florical® contains 3.75 mg fluoride (as sodium fluoride), 145 mg calcium (as calcium carbonate)

DIRECTIONS
Take one tablet or capsule daily, or as recommended by physician.

HOW SUPPLIED
Florical® is supplied as tablets or capsules in bottles of 100 or 500.
NDC 00394-0102-02 (Capsules 100's)
NDC 00394-0102-05 (Capsules 500's)
NDC 00394-0100-02 (Tablets 100's)
NDC 00394-0100-05 (Tablets 500's)

MONOCAL® OTC
[*mon ō cal*]
(fluoride and calcium supplement)

ACTIVE INGREDIENTS
Monocal® contains 3 mg fluoride (as monofluorophosphate) and 250 mg calcium (as calcium carbonate)

DIRECTIONS
Take one tablet daily, or as recommended by physician.

HOW SUPPLIED
Monocal® is supplied as tablets in bottles of 100 & 500.
NDC 00394-0105-02
NDC 00394-0105-05

Merz Pharmaceuticals
DIVISION OF MERZ, INC.
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GREENSBORO, NC 27419

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Medical/Regulatory Affairs
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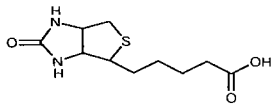
APPEAREX® OTC
(biotin 2.5 mg)

DESCRIPTION AND MECHANISM OF ACTION

Appearex® is a biotin preparation (2.5 mg) available for oral administration as a small, easy-to-swallow tablet. Each Appearex® tablet contains as its active ingredient 2.5 mg of biotin, a dose clinically proven to improve nail strength and quality.[1–4] Inactive ingredients include lactose monohydrate, cornstarch, povidone (K25), and magnesium stearate. Biotin is a water-soluble vitamin component of the vitamin B complex. As an essential nutrient, biotin acts as a coenzyme for the body's carboxylation reactions and is a factor in maintaining healthy muscle, hair, nails, and skin. Its molecular formula is $C_{10}H_{16}N_2O_3S$, and its molecular weight is 244.308. It has the following structural formula:



The presumed mechanism of action by which Appearex® affects brittle nails is via the pharmacologic effects of biotin on all keratin structures. Biotin stimulates the differentiation of epidermal cells and is involved in keratinization. It is also believed that biotin increases the quantity of keratin matrix proteins in the nail, thereby improving keratin structure.[3,5]

PHARMACOKINETICS

ABSORPTION AND TRANSPORT:
Biotin is efficiently absorbed in the small intestine sodium-mediated carrier transport.[6,7] Once absorbed, 80% of biotin is free, and the remaining 20% is bound to plasma proteins.[8] Cellular entry of biotin occurs by both diffusion and sodium-dependent transport.

DEGRADATION AND EXCRETION:
About 43% of biotin is excreted unchanged in the urine.[9] The remainder is excreted as degradation products including bisnorbiotin (30%), biotin sulfoxide (11%), and other small amounts of biotin sulfone, bisnorbiotin methylketone, and tetranorbiotin sulfoxide.[10]

ADVERSE REACTIONS

Adverse reactions associated with biotin supplementation are rare in the medical literature; however, urticaria and gastrointestinal upset have been reported. As with any oral treatment, if patients experience any adverse reactions or side effects, they should inform their physicians immediately and discontinue use.

DRUG INTERACTIONS

The anticonvulsants carbamazepine, phenytoin, phenobarbital, and primidone may accelerate biotin metabolism, leading to a reduction in available biotin. Chronic use of these drugs has been associated with decreased plasma concentrations of biotin.[11,12]

The use of antibiotics may reduce the contribution of biotin made by bacteria within the large intestine.

PRECAUTIONS AND WARNINGS

Pregnant women and nursing mothers should consult their physicians before taking this product. Appearex® should not be used in patients with known allergy or hypersensitivity to any of its ingredients.

TOXICITY

No toxic effects have been reported, even at higher doses.[13]

INDICATION AND USAGE

Appearex® is recommended for first-line treatment of weak, brittle, splitting, or soft nails.

Appearex® therapy should be taken regularly as directed to maintain strong, healthy nails. Clinical improvement is generally realized within 3 to 6 months.[1–3] Cessation of therapy may result in deterioration of nail health within 6 to 9 months.

CONTRAINDICATION

Appearex® is contraindicated in patients allergic or hypersensitive to any of its ingredients.

DOSAGE AND ADMINISTRATION

Recommended treatment for adults is 1 tablet taken daily with water. For use in children under 12 years of age, consult a physician for guidance regarding proper dosing and administration.

HOW SUPPLIED

One Appearex® package contains 30 tablets (1 month's supply) enclosed in blister packs.

SUMMARY

Appearex®, for the treatment of weak, brittle, splitting, or soft nails, is pharmaceutical grade oral biotin that restores nail quality by promoting keratinization. It has been clinically proven to increase nail plate thickness, smooth brittle nail ridges, and improve overall nail quality. As a water-soluble essential vitamin the biotin in Appearex® is safe and well tolerated. For patients with brittle nails, one Appearex® tablet taken daily provides the additional biotin needed to manage onychoschizia/onychorrhexis.

These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

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Continued on next page

Appearex—Cont.

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5010814 Rev 05/04

ELDERTONIC® **OTC**
(Multi-vitamin)

INDICATIONS
B-complex vitamins with minerals for nutritional supplementation.

DOSAGE
Adults: one tablespoon (15 mL) three times daily just before meals.

WARNING
Do not exceed recommended dosage unless directed by a physician.

USAGE IN PREGNANCY
Safe use of this product in pregnancy has not been established.

CAUTION
Keep out of the reach of children.

HOW SUPPLIED
ELDERTONIC is available in 16 fl. oz. bottles: #5010444.

Supplement Facts

Serving Size 1 tablespoon (15 mL)
Servings Per Container 31

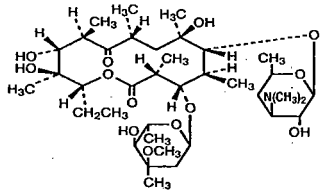
	Amount Per Serving	% Daily Value
Calories	35	
Total Carbohydrates	5g	1%*
Sugar	4g	†
Thiamin HCl (Vitamin B1)	0.5mg	33%
Riboflavin (Vitamin B2)	0.6mg	33%
Niacin	7mg	33%
Vitamin B6	0.7mg	33%
Vitamin B12	2mcg	33%
Pantothenic Acid	3mg	33%
Magnesium	0.7mg	< 1%
Zinc	5mg	33%
Manganese	0.7mg	33%

*Percent daily value based on a 2000 calorie diet
†Daily value not established Alcohol content 13.5%

Other ingredients: sherry wine, sucrose, sorbitol, FD&C red #40, purified water
30-1113-01 Rev. 08/03

ERYGEL® ℞
ERYTHROMYCIN
TOPICAL GEL USP 2%
Rx Only
For Dermatologic Use Only-Not for Ophthalmic Use-

DESCRIPTION
ERYGEL® Topical Gel contains erythromycin ((3R*, 4S*, 5S*, 6R*, 7R*, 9R*, 11R*, 12R*, 13S*, 14R*)-4-[(2, 6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7, 12, 13-trihydroxy-3, 5, 7, 9, 11, 13-hexamethyl-6-[[3, 4, 6,-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl] oxy] oxacyclotetradecane-2, 10-dione), for topical dermatological use. Erythromycin is a macrolide antibiotic produced from a strain of *Saccaropolyspora erythraea* (formerly *Streptomyces erythreus*). It is a base and readily forms salts with acids.
Chemically, erythromycin is $C_{37}H_{67}NO_{13}$. It has the following structural formula:



Erythromycin has a molecular weight of 733.94. It is a white or slightly yellow, odorless or practically odorless, bitter crystalline powder. Erythromycin is very soluble in very polar organic solvents such as alcohols, acetone, chloroform, acetonitrile and ethyl acetate. It is moderately soluble in less polar solvents such as ether, dichloroethylene and amyl acetate. It is slightly soluble in nonpolar solvents such as hexane. It is very poorly soluble in water.
Each gram of ERYGEL® Topical Gel contains 20 mg of erythromycin, USP in a base of alcohol 92% and hydroxypropyl cellulose.

CLINICAL PHARMACOLOGY
The exact mechanism by which erythromycin reduces lesions of acne vulgaris is not fully known; however, the effect appears to be due in part to the antibacterial activity of the drug.

MICROBIOLOGY
Erythromycin acts by inhibition of protein synthesis in susceptible organisms by reversibly binding to 50S ribosomal subunits, thereby inhibiting translocation of aminoacyl transfer-RNA and inhibiting polypeptide synthesis. Antagonism has been demonstrated *in vitro* between erythromycin, lincomycin, chloramphenicol, and clindamycin.

INDICATIONS AND USAGE
ERYGEL® Topical Gel is indicated for the topical treatment of acne vulgaris.

CONTRAINDICATIONS
ERYGEL® Topical Gel is contraindicated in those individuals who have shown hypersensitivity to any of its components.

WARNINGS
Pseudomembranous colitis has been reported with nearly all antibacterial agents, including erythromycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.
Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis".
After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

PRECAUTIONS
General: For topical use only; not for ophthalmic use. Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating or abrasive agents.
The use of antibiotic agents may be associated with the overgrowth of antibiotic-resistant organisms. If this occurs, discontinue use and take appropriate measures.
Avoid contact with eyes and all mucous membranes.
Information For Patients: Patients using ERYGEL® Topical Gel should receive the following information and instructions:
1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes, nose, mouth, and all mucous membranes.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. Patients should not use any other topical acne medication unless otherwise directed by their physician.
4. Patients should report to their physician any signs of local adverse reactions.

Carcinogenesis, mutagenesis, impairment of fertility: No animal studies have been performed to evaluate carcinogenic and mutagenic potential or effects on fertility of topical erythromycin. However, long-term (2-year) oral studies in rats with erythromycin ethylsuccinate and erythromycin base did not provide evidence of tumorigenicity. There was no apparent effect on male or female fertility in rats fed erythromycin (base) at levels up to 0.25% of diet.
Pregnancy: Teratogenic effects: Pregnancy Category B: There was no evidence of teratogenicity or any other adverse effect on reproduction in female rats fed erythromycin base (up to 0.25% of diet) prior to and during mating, during gestation and through weaning of two successive litters. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used in pregnancy only if clearly needed. Erythromycin has been reported to cross the placental barrier in humans, but fetal plasma levels are generally low.
Nursing women: It is not known whether erythromycin is excreted in human milk after topical application. However, erythromycin is excreted in human milk following oral and parenteral erythromycin administration. Therefore, caution should be exercised when erythromycin is administered to a nursing woman.
Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS
In controlled clinical trials, the incidence of burning associated with ERYGEL® Topical Gel was approximately 25%. The following additional local adverse reactions have been reported occasionally: peeling, dryness, itching, erythema, and oiliness. Irritation of the eyes and tenderness of the skin have also been reported with the topical use of erythromycin. A generalized urticarial reaction, possibly related to the use of erythromycin, which required systemic steroid therapy has been reported.

DOSAGE AND ADMINISTRATION
ERYGEL® Topical Gel should be applied sparingly as a thin film to affected area(s) once or twice a day after the skin is thoroughly cleansed and patted dry. If there has been no improvement after 6 to 8 weeks, or if the condition becomes worse, treatment should be discontinued, and the physician should be reconsulted. Spread the medication lightly rather than rubbing it in. There are no data directly comparing the safety and efficacy of b.i.d. versus q.d. dosing.

HOW SUPPLIED
ERYGEL® (Erythromycin Topical Gel USP) 2% is supplied in plastic tubes in the following sizes:
30g - NDC 0259-4312-30 and 60 g - NDC 0259-4312-60.
Note: FLAMMABLE. Keep away from heat and flame. Store and dispense in original container. Keep tube tightly closed.
Store between 15° and 25°C (59° and 77°F).
Manufactured for: **Merz Pharmaceuticals, Greensboro, NC 27410**
70-2057-00 Rev 10/01

MEDERMA® **OTC**
[*mə-der-mă*]
allium cepa
Skin Care for Scars™

DESCRIPTION
HELPS THE APPEARANCE OF SCARS RESULTING FROM: Surgery, Burns, Injury, Acne, Stretch Marks
Mederma® is a topical gel formulated to benefit anyone with new scars or existing scars. Mederma® is a greaseless, pleasant-smelling topical gel that not only helps scars appear softer and smoother, but also offers convenience, ease of use and affordability.

INGREDIENTS
Water (Purified), PEG-4, Allium Cepa (Onion) Bulb Extract, Xanthan Gum, Allantoin, Fragrance, Methylparaben, Sorbic Acid.

DOSAGE AND ADMINISTRATION
Gently massage Mederma® into the scar or stretch marks 3 to 4 times daily. Mederma should be used for 8 weeks on new scars and 2–6 months on existing scars and stretch marks.
NOT INTENDED FOR USE ON OPEN WOUNDS
FOR TOPICAL USE ONLY

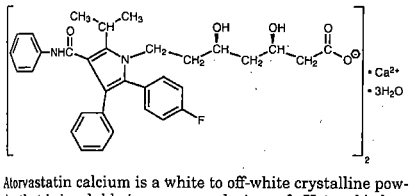
STORAGE
Store at room temperature

HOW SUPPLIED
Mederma® is supplied in 20g (#30928) and 50g (#30472) tubes. The 20g tube will last approximately 3 months when treating a scar up to 3 inches in length. The 50g tube will last approximately 3 months when treating a scar 8 to 10 inches in length.
Manufactured for: Merz Pharmaceuticals, Greensboro, NC 27410
30-2065-01 Rev. 06/04

LIPITOR® ℞
[li'pi-tōr]
(Atorvastatin Calcium)
Tablets

DESCRIPTION

Lipitor® (atorvastatin calcium) is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis. Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca \cdot 3H_2O$ and its molecular weight is 1209.42. Its structural formula is:



Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.

Lipitor tablets for oral administration contain 10, 20, 40 or 80 mg atorvastatin and the following inactive ingredients: calcium carbonate, USP; candelilla wax, FCC; croscarmellose sodium, NF; hydroxypropyl cellulose, NF; lactose monohydrate, NF; magnesium stearate, NF; microcrystalline cellulose, NF; Opadry White YS-1-7040 (hypromellose, polyethylene glycol, talc, titanium dioxide); polysorbate 80, NF; simethicone emulsion.

CLINICAL PHARMACOLOGY

Mechanism of Action

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

In animal models, Lipitor lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL; Lipitor also reduces LDL production and the number of LDL particles. Lipitor reduces LDL-C in some patients with homozygous familial hypercholesterolemia (FH), a population that rarely responds to other lipid-lowering medication(s).

A variety of clinical studies have demonstrated that elevated levels of total-C, LDL-C, and apo B (a membrane complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of HDL-C (and its transport complex, apo A) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C, and inversely with the level of HDL-C.

Lipitor reduces total-C, LDL-C, and apo B in patients with homozygous and heterozygous FH, nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. Lipitor also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-1. Lipitor reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridemia. Lipitor reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate density lipoprotein (IDL), and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

Pharmacodynamics

Atorvastatin as well as some of its metabolites are pharmacologically active in humans. The liver is the primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dosage rather than systemic drug concentration correlates better with LDL-C reduction. Individualization of drug dosage should be based on therapeutic response (see DOSAGE AND ADMINISTRATION).

TABLE 1. Dose-Response in Patients With Primary Hypercholesterolemia (Adjusted Mean % Change From Baseline)[a]

Dose	N	TC	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Placebo	21	4	4	3	10	-3	7
10	22	-29	-39	-32	-19	6	-34
20	20	-33	-43	-35	-26	9	-41
40	21	-37	-50	-42	-29	6	-45
80	23	-45	-60	-50	-37	5	-53

[a]Results are pooled from 2 dose-response studies.

Pharmacokinetics and Drug Metabolism

Absorption: Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by Cmax and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration (see DOSAGE AND ADMINISTRATION).

Distribution: Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin is likely to be secreted in human milk (see CONTRAINDICATIONS, Pregnancy and Lactation, and PRECAUTIONS, Nursing Mothers).

Metabolism: Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following coadministration with erythromycin, a known inhibitor of this isozyme (see PRECAUTIONS, Drug Interactions). In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion: Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

Special Populations

Geriatric: Plasma concentrations of atorvastatin are higher (approximately 40% for Cmax and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults. Clinical data suggest a greater degree of LDL-lowering at any dose of drug in the elderly patient population compared to younger adults (see PRECAUTIONS section; Geriatric Use subsection).

Pediatric: Pharmacokinetic data in the pediatric population are not available.

Gender: Plasma concentrations of atorvastatin in women differ from those in men (approximately 20% higher for Cmax and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with Lipitor between men and women.

Renal Insufficiency: Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin; thus, dose adjustment in patients with renal dysfunction is not necessary (see DOSAGE AND ADMINISTRATION).

Hemodialysis: While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of atorvastatin since the drug is extensively bound to plasma proteins.

Hepatic Insufficiency: In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. Cmax and AUC are each 4-fold greater in patients with Childs-Pugh A disease. Cmax and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease (see CONTRAINDICATIONS).

Clinical Studies

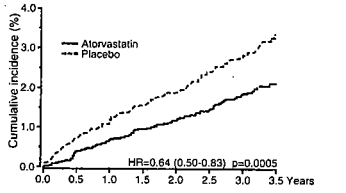
Prevention of Cardiovascular Disease

In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of LIPITOR (atorvastatin calcium) on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 40-80 years of age (mean of 63 years), without a previous myocardial infarction and with TC levels ≤251 mg/dl (6.5 mmol/l). Additionally all patients had at least 3 of the following cardiovascular risk factors: male gender (81.1%), age >55 years (84.5%), smoking (33.2%), diabetes (24.3%), history of CHD in a first-degree relative (26%), TC:HDL >6 (14.3%), peripheral vascular disease (5.1%), left ventricular hypertrophy (14.4%), prior cerebrovascular event (9.8%), specific ECG abnormality (14.3%), proteinuria/albuminuria (62.4%)]. In this double-blind, placebo-controlled study patients were treated with anti-hypertensive therapy (Goal BP <140/90 mm Hg for non-diabetic patients, <130/80 mm Hg for diabetic patients) and allocated to either LIPITOR 10 mg daily (n=5168) or placebo (n=5137), using a covariate adaptive method which took into account the distribution of fourteen baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups. Patients were followed for a median duration of 3.3 years.

The effect of 10 mg/day of LIPITOR on lipid levels was similar to that seen in previous clinical trials.

LIPITOR significantly reduced the rate of coronary events [either fatal coronary heart disease (46 events in the placebo group vs 40 events in the LIPITOR group) or nonfatal MI (108 events in the placebo group vs 60 events in the LIPITOR group)] with a relative risk reduction of 36% [(based on incidences of 1.9% for LIPITOR vs 3.0% for placebo), p=0.0005 (see Figure 1)]. The risk reduction was consistent regardless of age, smoking status, obesity or presence of renal dysfunction. The effect of LIPITOR was seen regardless of baseline LDL levels. Due to the small number of events, results for women were inconclusive.

Figure 1: Effect of LIPITOR 10 mg/day on Cumulative Incidence of Nonfatal Myocardial Infarction or Coronary Heart Disease Death (in ASCOT-LLA)



LIPITOR also significantly decreased the relative risk for revascularization procedures by 42%. Although the reduction of fatal and non-fatal strokes did not reach a predefined significance level (p = 0.01), a favorable trend was observed with a 26% relative risk reduction (incidences of 1.7% for LIPITOR and 2.3% for placebo). There was no significant difference between the treatment groups for death due to cardiovascular causes (p=0.51) or noncardiovascular causes (p=0.17).

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (*Fredrickson* Types IIa and IIb)

Lipitor reduces total-C, LDL-C, VLDL-C, apo B, and TG, and increases HDL-C in patients with hypercholesterolemia and mixed dyslipidemia. Therapeutic response is seen within 2 weeks, and maximum response is usually achieved within 4 weeks and maintained during chronic therapy.

Lipitor is effective in a wide variety of patient populations with hypercholesterolemia, with and without hypertriglyceridemia, in men and women, and in the elderly. Experience in pediatric patients has been limited to patients with homozygous FH. In two multicenter, placebo-controlled, dose-response studies in patients with hypercholesterolemia, Lipitor given as a single dose over 6 weeks significantly reduced total-C, LDL-C, apo B, and TG (Pooled results are provided in Table 1).

[See table 1 above]

In patients with *Fredrickson* Types IIa and IIb hyperlipoproteinemia pooled from 24 controlled trials, the median (25th and 75th percentile) percent changes from baseline in HDL-C for atorvastatin 10, 20, 40, and 80 mg were 6.4 (-1.4, 14), 8.7 (0, 17), 7.8 (0, 16), and 5.1 (-2.7, 15), respectively. Additionally, analysis of the pooled data demonstrated consistent and significant decreases in total-C, LDL-C, TG, total-C/HDL-C, and LDL-C/HDL-C.

In three multicenter, double-blind studies in patients with hypercholesterolemia, Lipitor was compared to other HMG-CoA reductase inhibitors. After randomization, patients were treated for 16 weeks with either Lipitor 10 mg per day or a fixed dose of the comparative agent (Table 2).

[See table 2 at top of next page]

The impact on clinical outcomes of the differences in lipid-altering effects between treatments shown in Table 2 is not known. Table 2 does not contain data comparing the effects of atorvastatin 10 mg and higher doses of lovastatin, prav-

Continued on next page

Lipitor—Cont.

astatin, and simvastatin. The drugs compared in the studies summarized in the table are not necessarily interchangeable.

Hypertriglyceridemia (*Fredrickson* Type IV)

The response to Lipitor in 64 patients with isolated hypertriglyceridemia treated across several clinical trials is shown in the table below. For the atorvastatin-treated patients, median (min, max) baseline TG level was 565 (267-1502).

[See table 3 at right]

Dysbetalipoproteinemia (*Fredrickson* Type III)

The results of an open-label crossover study of 16 patients (genotypes: 14 apo E2/E2 and 2 apo E3/E2) with dysbetalipoproteinemia (*Fredrickson* Type III) are shown in the table below.

[See table 4 below]

Homozygous Familial Hypercholesterolemia

In a study without a concurrent control group, 29 patients ages 6 to 37 years with homozygous FH received maximum daily doses of 20 to 80 mg of Lipitor. The mean LDL-C reduction in this study was 18%. Twenty-five patients with a reduction in LDL-C had a mean response of 20% (range of 7% to 53%, median of 24%); the remaining 4 patients had 7% to 24% increases in LDL-C. Five of the 29 patients had absent LDL-receptor function. Of these, 2 patients also had a portacaval shunt and had no significant reduction in LDL-C. The remaining 3 receptor-negative patients had a mean LDL-C reduction of 22%.

Heterozygous Familial Hypercholesterolemia in Pediatric Patients

In a double-blind, placebo-controlled study followed by an open-label phase, 187 boys and postmenarchal girls 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia (FH) or severe hypercholesterolemia were randomized to Lipitor (n=140) or placebo (n=47) for 26 weeks and then all received Lipitor for 26 weeks. Inclusion in the study required 1) a baseline LDL-C level ≥ 190 mg/dL or 2) a baseline LDL-C ≥ 160 mg/dL and positive family history of FH or documented premature cardiovascular disease in a first- or second-degree relative. The mean baseline LDL-C value was 218.6 mg/dL (range: 138.5-385.0 mg/dL) in the Lipitor group compared to 230.0 mg/dL (range: 160.0-324.5 mg/dL) in the placebo group. The dosage of Lipitor (once daily) was 10 mg for the first 4 weeks and up-titrated to 20 mg if the LDL-C level was > 130 mg/dL. The number of Lipitor-treated patients who required up-titration to 20 mg after Week 4 during the double-blind phase was 80 (57.1%).

Lipitor significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26 week double-blind phase (see Table 5).

[See table 5 at right]

The mean achieved LDL-C value was 130.7 mg/dL (range: 70.0-242.0 mg/dL) in the Lipitor group compared to 228.5 mg/dL (range: 152.0-385.0 mg/dL) in the placebo group during the 26 week double-blind phase.

The safety and efficacy of doses above 20 mg have not been studied in controlled trials in children. The long-term efficacy of Lipitor therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

INDICATIONS AND USAGE

Prevention of Cardiovascular Disease

In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age ≥ 55 years, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, Lipitor is indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk for revascularization procedures and angina

Hypercholesterolemia

Lipitor is indicated:

1. as an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (*Fredrickson* Types IIa and IIb);
2. as an adjunct to diet for the treatment of patients with elevated serum TG levels (*Fredrickson* Type IV);
3. for the treatment of patients with primary dysbetalipoproteinemia (*Fredrickson* Type III) who do not respond adequately to diet;
4. to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (eg, LDL apheresis) or if such treatments are unavailable;
5. as an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:
   a. LDL-C remains ≥ 190 mg/dL or
   b. LDL-C remains ≥ 160 mg/dL and:
      - there is a positive family history of premature cardiovascular disease or
      - two or more other CVD risk factors are present in the pediatric patient

Therapy with lipid-altering agents should be a component of multiple-risk-factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol only when the response to diet and other nonpharmacological measures has been inadequate (see *National Cholesterol Education Program (NCEP) Guidelines*, summarized in Table 6).

[See table 6 above]

After the LDL-C goal has been achieved, if the TG is still ≥200 mg/dL, non HDL-C (total-C minus HDL-C) becomes a secondary target of therap 30 mg/dL higher than LDL- Prior to initiating therapy w hypercholesterolemia (eg, p tus, hypothyroidism, nephro obstructive liver disease, ot ism) should be excluded, a measure total-C, LDL-C, HI TG <400 mg/dL (<4.5 mmol ing the following equation: I HDL-C). For TG levels >4 equation is less accurate an be determined by ultracentr Lipitor has not been studied lipoprotein abnormality i (*Fredrickson* Types I and V) The NCEP classification of c tients with a familial histo premature cardiovascular di

TABLE 2. Mean Percent Change From Baseline at End Point (Double-Blind, Randomized, Active-Controlled Trials)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Study 1							
Atorvastatin 10 mg	707	-27[a]	-36[a]	-28[a]	-17[a]	+7	-37[a]
Lovastatin 20 mg	191	-19	-27	-20	-6	+7	-28
95% CI for Diff[1]		-9.2, -6.5	-10.7, -7.1	-10.0, -6.5	-15.2, -7.1	-1.7, 2.0	-11.1, -7.1
Study 2							
Atorvastatin 10 mg	222	-25[b]	-35[b]	-27[b]	-17[b]	+6	-36[b]
Pravastatin 20 mg	77	-17	-23	-17	-9	+8	-28
95% CI for Diff[1]		-10.8, -6.1	-14.5, -8.2	-13.4, -7.4	-14.1, -0.7	-4.9, 1.6	-11.5, -4.1
Study 3							
Atorvastatin 10 mg	132	-29[c]	-37[c]	-34[c]	-23[c]	+7	-39[c]
Simvastatin 10 mg	45	-24	-30	-30	-15	+7	-33
95% CI for Diff[1]		-8.7, -2.7	-10.1, -2.6	-8.0, -1.1	-15.1, -0.7	-4.3, 3.9	-9.6, -1.9

[1] A negative value for the 95% CI for the difference between treatments favors atorvastatin for all except HDL-C, for which a positive value favors atorvastatin. If the range does not include 0, this indicates a statistically significant difference.
[a] Significantly different from lovastatin, ANCOVA, p ≤0.05
[b] Significantly different from pravastatin, ANCOVA, p ≤0.05
[c] Significantly different from simvastatin, ANCOVA, p ≤0.05

TABLE 3. Combined Patients With Isolated Elevated TG: Median (min, max) Percent Changes From Baseline

	Placebo (N=12)	Atorvastatin 10 mg (N=37)	Atorvastatin 20 mg (N=13)	Atorvastatin 80 mg (N=14)
Triglycerides	-12.4 (-36.6, 82.7)	-41.0 (-76.2, 49.4)	-38.7 (-62.7, 29.5)	-51.8 (-82.8, 41.3)
Total-C	-2.3 (-15.5, 24.4)	-28.2 (-44.9, -6.8)	-34.9 (-49.6, -15.2)	-44.4 (-63.5, -3.8)
LDL-C	3.6 (-31.3, 31.6)	-26.5 (-57.7, 9.8)	-30.4 (-53.9, 0.3)	-40.5 (-60.6, -13.8)
HDL-C	3.8 (-18.6, 13.4)	13.8 (-9.7, 61.5)	11.0 (-3.2, 25.2)	7.5 (-10.8, 37.2)
VLDL-C	-1.0 (-31.9, 53.2)	-48.8 (-85.8, 57.3)	-44.6 (-62.2, -10.8)	-62.0 (-88.2, 37.6)
non-HDL-C	-2.8 (-17.6, 30.0)	-33.0 (-52.1, -13.3)	-42.7 (-53.7, -17.4)	-51.5 (-72.9, -4.3)

TABLE 4. Open-Label Crossover Study of 16 Patients With Dysbetalipoproteinemia (*Fredrickson* Type III)

		Median % Change (min, max)	
	Median (min, max) at Baseline (mg/dL)	Atorvastatin 10 mg	Atorvastatin 80 mg
Total-C	442 (225, 1320)	-37 (-85, 17)	-58 (-90, -31)
Triglycerides	678 (273, 5990)	-39 (-92, -8)	-53 (-95, -30)
IDL-C + VLDL-C	215 (111, 613)	-32 (-76, 9)	-63 (-90, -8)
non-HDL-C	411 (218, 1272)	-43 (-87, -19)	-64 (-92, -36)

TABLE 5
Lipid-altering Effects of Lipitor in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia or Severe Hypercholesterolemia
(Mean Percent Change from Baseline at Endpoint in Intention-to-Treat Population)

DOSAGE	N	Total-C	LDL-C	HDL-C	TG	Apolipoprotein B
Placebo	47	-1.5	-0.4	-1.9	1.0	0.7
Lipitor	140	-31.4	-39.6	2.8	-12.0	-34.0

TABLE 6. NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD[a] or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional)[b]
2+ Risk Factors (10-year risk ≤20%)	<130	≥130	10-year risk 10%-20%: ≥130 10-year risk <10%: ≥160
0-1 Risk factor[c]	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

[a] CHD, coronary heart disease
[b] Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.
[c] Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

Category	Total-C
Acceptable	<1
Borderline	170
High	≥2

CONTRAINDICATIONS

Active liver disease or unex serum transaminases.

Hypersensitivity to any com

Pregnancy and Lactation

Atherosclerosis is a chronic lipid-lowering drugs during impact on the outcome of lo percholesterolemia. Cholest lesterol biosynthesis are e development (including syn branes). Since HMG-CoA re lesterol synthesis and possib ically active substances der cause fetal harm when adr Therefore, HMG-CoA redu dicated during pregnanc ATORVASTATIN SHOUL WOMEN OF CHILDBEAR PATIENTS ARE HIGHLY AND HAVE BEEN INFO HAZARDS. If the patient this drug, therapy should b apprised of the potential ha

WARNINGS

Liver Dysfunction

HMG-CoA reductase inhibit ing therapies, have been ass malities of liver function. **the upper limit of normal (t casions) in serum transam tients who received atorva dence of these abnormalit 2.3% for 10, 20, 40, and 80** One patient in clinical tria in liver function tests (LFT sociated with jaundice or o Upon dose reduction, drug transaminase levels return without sequelae. Eighteer LFT elevations continued t atorvastatin.

It is recommended that liv prior to and at 12 weeks therapy and any elevatior semiannually) thereafter. I occur in the first 3 months Patients who develop incre be monitored until the abn crease in ALT or AST of >3 dose or withdrawal of atorv Atorvastatin should be us consume substantial quant tory of liver disease. Active sistent transaminase eleva use of atorvastatin (see CC

Skeletal Muscle

Rare cases of rhabdomy secondary to myoglobin atorvastatin and with othe Uncomplicated myalgia ha treated patients (see ADV defined as muscle aches or with increases in creatine times ULN, should be consi myalgias, muscle tenderne elevation of CPK. Patien promptly unexplained mu ness, particularly if acco Atorvastatin therapy shoul evated CPK levels occur suspected.

The risk of myopathy duri class is increased with con sporine, fibric acid deriva azole antifungals. Physicia

secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

Prior to initiating therapy with Lipitor, secondary causes for hypercholesterolemia (eg, poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, and alcoholism) should be excluded, and a lipid profile performed to measure total-C, LDL-C, HDL-C, and TG. For patients with TG <400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation: LDL-C = total-C - (0.20 × [TG] + HDL-C). For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation.

Lipitor has not been studied in conditions where the major lipoprotein abnormality is elevation of chylomicrons (*Fredrickson* Types I and V).

The NCEP classification of cholesterol levels in pediatric patients with a familial history of hypercholesterolemia or premature cardiovascular disease is summarized below:

Category	Total-C (mg/dL)	LDL-C (mg/dL)
Acceptable	<170	<110
Borderline	170-199	110-129
High	≥200	≥130

CONTRAINDICATIONS

Active liver disease or unexplained persistent elevations of serum transaminases.

Hypersensitivity to any component of this medication.

Pregnancy and Lactation

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. ATORVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Dysfunction

HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.**

One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin.

It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (eg, semiannually) thereafter. Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of atorvastatin is recommended.

Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin (see CONTRAINDICATIONS).

Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class.

Uncomplicated myalgia has been reported in atorvastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-lowering doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (eg, severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

PRECAUTIONS

General

Before instituting therapy with atorvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

Information for Patients

Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Drug Interactions

The risk of myopathy during treatment with drugs of this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, niacin (nicotinic acid), erythromycin, azole antifungals (see WARNINGS, Skeletal Muscle).

Antacid: When atorvastatin and Maalox® TC suspension were coadministered, plasma concentrations of atorvastatin decreased approximately 35%. However, LDL-C reduction was not altered.

Antipyrine: Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Colestipol: Plasma concentrations of atorvastatin decreased approximately 25% when colestipol and atorvastatin were coadministered. However, LDL-C reduction was greater when atorvastatin and colestipol were coadministered than when either drug was given alone.

Cimetidine: Atorvastatin plasma concentrations and LDL-C reduction were not altered by coadministration of cimetidine.

Digoxin: When multiple doses of atorvastatin and digoxin were coadministered, steady-state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately.

Erythromycin: In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with coadministration of atorvastatin and erythromycin, a known inhibitor of cytochrome P450 3A4 (see WARNINGS, Skeletal Muscle).

Oral Contraceptives: Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

Warfarin: Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if an HMG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

CNS Toxicity

Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0-24) based on the maximum recommended human dose of 80 mg/day.

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose.

A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

In vitro, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test.

Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years.

Pregnancy

Pregnancy Category X

See CONTRAINDICATIONS

Safety in pregnant women has not been established. Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m^2).

In a study in rats given 20, 100, or 225 mg/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity in pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 in pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day. Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took lovastatin with dextroamphetamine sulfate during the first trimester of pregnancy. Lipitor should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking Lipitor, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers

Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Because of the potential for adverse reactions in nursing infants, women taking Lipitor should not breast-feed (see CONTRAINDICATIONS).

Pediatric Use

Safety and effectiveness in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial of 6 months duration in adolescent boys and postmenarchal girls. Patients treated with Lipitor had an adverse experience profile generally similar to that of patients treated with placebo, the most common adverse experiences observed in both groups, regardless of causality assessment, were infections. **Doses greater than 20 mg have not been studied in this patient population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in boys or on menstrual cycle length in girls (see CLINICAL PHARMACOLOGY, Clinical Studies section; ADVERSE REACTIONS, Pediatric Patients (ages 10-17 years); and DOSAGE AND ADMINISTRATION, Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age). Adolescent females should be counseled on appropriate contraceptive methods while on Lipitor therapy (see CONTRAINDICATIONS and PRECAUTIONS, Pregnancy). **Lipitor has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.**

Continued on next page

Lipitor—Cont.

Clinical efficacy with doses up to 80 mg/day for 1 year have been evaluated in an uncontrolled study of patients with homozygous FH including 8 pediatric patients (see CLINICAL PHARMACOLOGY, Clinical Studies: Homozygous Familial Hypercholesterolemia).

Geriatric Use

The safety and efficacy of atorvastatin (10-80 mg) in the geriatric population (≥65 years of age) was evaluated in the ACCESS study. In this 54-week open-label trial 1,958 patients initiated therapy with atorvastatin 10 mg. Of these, 835 were elderly (≥65 years) and 1,123 were non-elderly. The mean change in LDL-C from baseline after 6 weeks of treatment with atorvastatin 10 mg was –38.2% in the elderly patients versus –34.6% in the non-elderly group.

The rates of discontinuation due to adverse events were similar between the two age groups. There were no differences in clinically relevant laboratory abnormalities between the age groups.

ADVERSE REACTIONS

Lipitor is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies of 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to atorvastatin. The most frequent adverse events thought to be related to atorvastatin were constipation, flatulence, dyspepsia, and abdominal pain.

Clinical Adverse Experiences

Adverse experiences reported in ≥2% of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment, are shown in Table 7.

[See table 7 below]

Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)

In ASCOT (see CLINICAL PHARMACOLOGY, *Clinical Studies*) involving 10,305 participants treated with Lipitor 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with Lipitor was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up.

The following adverse events were reported, regardless of causality assessment in patients treated with atorvastatin in clinical trials. The events in italics occurred in ≥2% of patients and the events in plain type occurred in <2% of patients.

Body as a Whole: *Chest pain,* face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema.

Digestive System: *Nausea,* gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice.

Respiratory System: *Bronchitis, rhinitis,* pneumonia, dyspnea, asthma, epistaxis.

Nervous System: *Insomnia, dizziness,* paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia, depression, hypesthesia, hypertonia.

Musculoskeletal System: *Arthritis,* leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis.

Skin and Appendages: Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer.

Urogenital System: *Urinary tract infection,* urinary frequency, cystitis, hematuria, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, albuminuria, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage.

Special Senses: Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion.

Cardiovascular System: Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia, angina pectoris, hypertension.

Metabolic and Nutritional Disorders: *Peripheral edema,* hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia.

Hemic and Lymphatic System: Ecchymosis, anemia, lymphadenopathy, thrombocytopenia, petechia.

Postintroduction Reports

Adverse events associated with Lipitor therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), and rhabdomyolysis.

Pediatric Patients (ages 10-17 years)

In a 26-week controlled study in boys and postmenarchal girls (n=140), the safety and tolerability profile of Lipitor 10 to 20 mg daily was generally similar to that of placebo (see CLINICAL PHARMACOLOGY, Clinical Studies section and PRECAUTIONS, Pediatric Use).

OVERDOSAGE

There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving Lipitor and should continue on this diet during treatment with Lipitor.

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (*Fredrickson* Types IIa and IIb)

The recommended starting dose of Lipitor is 10 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of Lipitor is 10 to 80 mg once daily. Lipitor can be administered as a single dose at any time of the day, with or without food. The starting dose and maintenance doses of Lipitor should be individualized according to patient characteristics such as goal of therapy and response (see *NCEP Guidelines,* summarized in Table 5). After initiation and/or upon titration of Lipitor, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should total-C be used to monitor therapy.

Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age)

The recommended starting dose of Lipitor is 10 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy (see NCEP Pediatric Panel Guidelines[1], CLINICAL PHARMACOLOGY, and INDICATIONS AND USAGE). Adjustments should be made at intervals of 4 weeks or more.

[1] National Cholesterol Education Program (NCEP): Highlights of the Report of the Expert Panel on Blood Cholesterol Levels in Children Adolescents, *Pediatrics*. 89(3):495-501. 1992.

Homozygous Familial Hypercholesterolemia

The dosage of Lipitor in patients with homozygous FH is 10 to 80 mg daily. Lipitor should be used as an adjunct to other lipid-lowering treatments (eg, LDL apheresis) in these patients or if such treatments are unavailable.

TABLE 7. Adverse Events in Placebo-Controlled Studies (% of Patients)

BODY SYSTEM/ Adverse Event	Placebo N = 270	Atorvastatin 10 mg N = 863	Atorvastatin 20 mg N = 36	Atorvastatin 40 mg N = 79	Atorvastatin 80 mg N = 94
BODY AS A WHOLE					
Infection	10.0	10.3	2.8	10.1	7.4
Headache	7.0	5.4	16.7	2.5	6.4
Accidental Injury	3.7	4.2	0.0	1.3	3.2
Flu Syndrome	1.9	2.2	0.0	2.5	3.2
Abdominal Pain	0.7	2.8	0.0	3.8	2.1
Back Pain	3.0	2.8	0.0	3.8	1.1
Allergic Reaction	2.6	0.9	2.8	1.3	0.0
Asthenia	1.9	2.2	0.0	3.8	0.0
DIGESTIVE SYSTEM					
Constipation	1.8	2.1	0.0	2.5	1.1
Diarrhea	1.5	2.7	0.0	3.8	5.3
Dyspepsia	4.1	2.3	2.8	1.3	2.1
Flatulence	3.3	2.1	2.8	1.3	1.1
RESPIRATORY SYSTEM					
Sinusitis	2.6	2.8	0.0	2.5	6.4
Pharyngitis	1.5	2.5	0.0	1.3	2.1
SKIN AND APPENDAGES					
Rash	0.7	3.9	2.8	3.8	1.1
MUSCULOSKELETAL SYSTEM					
Arthralgia	1.5	2.0	0.0	5.1	0.0
Myalgia	1.1	3.2	5.6	1.3	0.0

Concomitant Therapy

Atorvastatin may be used in combination with a bile acid binding resin for additive effect. The combination of HMG-CoA reductase inhibitors and fibrates should generally be avoided (see WARNINGS, Skeletal Muscle, and PRECAUTIONS, Drug Interactions for other drug-drug interactions).

Dosage in Patients With Renal Insufficiency

Renal disease does not affect the plasma concentrations nor LDL-C reduction of atorvastatin; thus, dosage adjustment in patients with renal dysfunction is not necessary (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

HOW SUPPLIED

Lipitor is supplied as white, elliptical, film-coated tablets of atorvastatin calcium containing 10, 20, 40 and 80 mg atorvastatin.

10 mg tablets: coded "PD 155" on one side and "10" on the other.
NDC 0071-0155-23 bottles of 90
NDC 0071-0155-34 bottles of 5000
NDC 0071-0155-40 10 × 10 unit dose blisters

20 mg tablets: coded "PD 156" on one side and "20" on the other.
NDC 0071-0156-23 bottles of 90
NDC 0071-0156-40 10 × 10 unit dose blisters
NDC 0071-0156-94 bottles of 5000

40 mg tablets: coded "PD 157" on one side and "40" on the other.
NDC 0071-0157-23 bottles of 90
NDC 0071-0157-73 bottles of 500

80 mg tablets: coded "PD 158" on one side and "80" on the other.
NDC 0071-0158-23 bottles of 90
NDC 0071-0158-73 bottles of 500

Storage

Store at controlled room temperature 20-25°C (68-77°F) [see USP].

Rx Only

Manufactured by:
Pfizer Ireland Pharmaceuticals
Dublin, Ireland
Distributed by:
Pfizer Parke-Davis
Division of Pfizer Inc, NY, NY 10017
LAB-0021-7.0 Revised July 2004

Shown in Product Identification Guide, page 328

NEURONTIN®

[nər-ŏn-tĭn]

(gabapentin) Capsules

NEURONTIN®

(gabapentin) Tablets

NEURONTIN®

(gabapentin) Oral Solution

DESCRIPTION

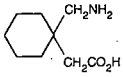
Neurontin® (gabapentin) Capsules, Neurontin® (gabapentin) Tablets, and Neurontin® (gabapentin) Oral Solution are supplied as imprinted hard shell capsules containing 100 mg, 300 mg, and 400 mg of gabapentin, elliptical film-coated tablets containing 600 mg and 800 mg of gabapentin or an oral solution containing 250 mg/5 mL of gabapentin.

The inactive ingredients for the capsules are lactose, cornstarch, and talc. The 100 mg capsule shell contains gelatin and titanium dioxide. The 300 mg capsule shell contains gelatin, titanium dioxide, and yellow iron oxide. The 400 mg capsule shell contains gelatin, red iron oxide, titanium dioxide, and yellow iron oxide. The imprinting ink contains FD&C Blue No. 2 and titanium dioxide.

The inactive ingredients for the tablets are poloxamer 407, copolyvidonum, cornstarch, magnesium stearate, hydroxypropyl cellulose, talc, candelilla wax and purified water.

The inactive ingredients for the oral solution are glycerin, xylitol, purified water and artificial cool strawberry anise flavor.

Gabapentin is described as 1-(aminomethyl)cyclohexaneacetic acid with a molecular formula of $C_9H_{17}NO_2$ and a molecular weight of 171.24. The structural formula of gabapentin is:



Gabapentin is a white to off-white crystalline solid with a pK_{a1} of 3.7 and a pK_{a2} of 10.7. It is freely soluble in water and both basic and acidic aqueous solutions. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is –1.25.

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism by which gabapentin exerts its analgesic action is unknown, but in animal models of analgesia, gabapentin prevents allodynia (pain-related behavior in response to a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful stimuli). In particular,

InnoPran XL—Cont.

Caution should be exercised when administering InnoPran XL with drugs that slow A-V nodal conduction, e.g., digitalis, lidocaine and calcium channel blockers.

Calcium Channel Blockers

Caution should be exercised when patients receiving a beta-blocker are administered a calcium-channel-blocking drug with negative inotropic and/or chronotropic effects. Both agents may depress myocardial contractility or atrioventricular conduction.

There have been reports of significant bradycardia, heart failure, and cardiovascular collapse with concurrent use of verapamil and beta-blockers.

Co-administration of propranolol and diltiazem in patients with cardiac disease has been associated with bradycardia, hypotension, high degree heart block, and heart failure.

Inotropic Agents

Patients on long-term therapy with propranolol may experience uncontrolled hypertension if administered epinephrine as a consequence of unopposed alpha-receptor stimulation. Epinephrine is therefore not indicated in the treatment of propranolol overdose (see OVERDOSAGE).

Isoproterenol and Dobutamine

Propranolol is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. Also, propranolol may reduce sensitivity to dobutamine stress echocardiography in patients undergoing evaluation for myocardial ischemia.

Reserpine

Patients receiving catecholamine-depleting drugs, such as reserpine and InnoPran XL, should be closely observed for excessive reduction of resting sympathetic nervous activity, which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension. Administration of reserpine with propranolol may also potentiate depression.

Non-Cardiovascular Drugs

Anesthetic Agents

Methoxyflurane and trichloroethylene may depress myocardial contractility when administered with propranolol.

Antidepressants

The hypotensive effects of MAO inhibitors or tricyclic antidepressants may be exacerbated when administered with beta-blockers by interfering with the beta-blocking activity of propranolol.

Neuroleptic Drugs

Hypotension and cardiac arrest have been reported with the concomitant use of propranolol and haloperidol.

Non-Steroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDS) have been reported to blunt the antihypertensive effect of beta-adrenoreceptor blocking agents.

Administration of indomethacin with propranolol may reduce the efficacy of propranolol in reducing blood pressure and heart rate.

Thyroxine

Thyroxine may result in a lower than expected T_3 concentration when used concomitantly with propranolol.

Warfarin

Propranolol when administered with warfarin increases the concentration of warfarin. Prothrombin time, therefore, should be monitored.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In dietary administration studies in which mice and rats were treated with propranolol for up to 18 months at doses of up to 150 mg/kg/day, there was no evidence of drug-related tumorigenesis. On a body surface area basis, this dose in the mouse and rat is, respectively, about equal to and about twice the maximum recommended human oral daily dose (MRHD) of 640 mg propranolol. In a study in which both male and female rats were exposed to propranolol in their diets at concentrations of up to 0.05% (about 50 mg/kg body weight and less than the MRHD), from 60 days prior to mating and throughout pregnancy and lactation for two generations, there were no effects on fertility. Based on differing results from Ames Tests performed by different laboratories, there is equivocal evidence for a genotoxic effect of propranolol in bacteria (S. typhimurium strain TA 1538).

Pregnancy: Pregnancy Category C

In a series of reproductive and developmental toxicology studies, propranolol was given to rats by gavage or in the diet throughout pregnancy and lactation. At doses of 150 mg/kg/day, but not at doses of 80 mg/kg/day (equivalent to the MRHD on a body surface area basis), treatment was associated with embryotoxicity (reduced litter size and increased resorption rates) as well as neonatal toxicity (deaths). Propranolol also was administered (in the feed) to rabbits (throughout pregnancy and lactation) at doses as high as 150 mg/kg/day (about 5 times the maximum recommended human oral daily dose). No evidence of embryo or neonatal toxicity was noted.

There are no adequate and well-controlled studies in pregnant women. Intrauterine growth retardation has been reported for neonates whose mothers received propranolol during pregnancy. Neonates whose mothers received propranolol at parturition have exhibited bradycardia, hypoglycemia, and respiratory depression. Adequate facilities for monitoring such infants at birth should be available. InnoPran XL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Propranolol is excreted in human milk. Caution should be exercised when InnoPran XL is administered to a nursing mother.

Pediatric Use

Safety and effectiveness of propranolol in pediatric patients have not been established.

Geriatric Use

Clinical studies of InnoPran XL did not include sufficient numbers of subjects ages 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Adverse events occurring at a rate of ≥3%, excluding those reported more commonly in placebo encountered in the InnoPran XL placebo-controlled hypertension trials and are plausibly related to treatment, are shown in Table 1.

Table 1. Treatment Emergent Adverse Events Reported In ≥ 3% of Subjects

	InnoPran XL		
Body System	**Placebo (N=88)**	**80 mg (N=89)**	**120 mg (N=85)**
Fatigue	3 (3.0%)	4 (5.0%)	6 (7.0%)
Dizziness (except vertigo)	2 (2.0%)	6 (7.0%)	3 (4.0%)
Constipation	0	3 (3.0%)	1 (1.0%)

The following adverse events were observed and have been reported with use of formulations of sustained- or immediate-release propranolol.

Cardiovascular: Bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Light-headedness, mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; vivid dreams; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. For immediate-release formulations, fatigue, lethargy, and vivid dreams appear dose related.

Gastrointestinal: Nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: Pharyngitis and agranulocytosis; erythematous rash, fever combined with aching and sore throat; laryngospasm, and respiratory distress.

Respiratory: Bronchospasm.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Autoimmune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: Alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes, and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION

InnoPran XL should be administered once daily at bedtime (approximately 10 PM) and should be taken consistently either on an empty stomach or with food. The starting dose is 80 mg but dosage should be individualized and titration may be needed to a dose of 120 mg. In the clinical trial, doses of InnoPran XL above 120 mg had no additional effects on blood pressure (See PHARMACODYNAMICS AND CLINICAL EFFECTS). The time needed for full antihypertensive response is variable, but is usually achieved within 2-3 weeks.

OVERDOSAGE

Most overdoses of propranolol are mild and respond to supportive care.

Propranolol is not significantly dialyzable. In the event of overdose or exaggerated response, the following measures should be employed:

Decontamination: Gastric lavage

Supportive Therapy

Hypotension and bradycardia have been reported following propranolol overdose and should be treated appropriately. Glucagon can exert potent inotropic and chronotropic effects and may be particularly useful for the treatment of hypotension or depressed myocardial function after a propranolol overdose.

Glucagon should be administered as 50-150 mcg/kg intravenously followed by continuous drip of 1-5 mg/hour for positive chronotropic effect. Isoproterenol,dopamine or phosphodiesterase inhibitors may also be useful. Epinephrine, however, may provoke uncontrolled hypertension. Bradycardia can be treated with atropine or isoproterenol. Serious bradycardia may require temporary cardiac pacing.

The electrocardiogram, pulse, blood pressure, neurobehavioral status and intake and output balance must be monitored. Isoproterenol and aminophylline may be used for bronchospasm.

HOW SUPPLIED

InnoPran XL (propranolol hydrochloride) Extended Release Capsules

Each gray/white capsule, imprinted with "80", 2 segmented bands, "RD201", and Reliant logo contains 80 mg of propranolol hydrochloride in bottles of 30 (NDC 65726-250-10), bottles of 100 (NDC 65726-250-25), bottles of 500 (NDC 65726-250-35), and a Unit Dose package of 100 (NDC 65726-250-90).

Each gray/off-white capsule, imprinted with "120", 3 segmented bands "InnoPran XL" and Reliant logo contains 120 mg of propranolol hydrochloride in bottles of 30 (NDC 65726-251-10), bottles of 100 (NDC 65726-251-25), bottles of 500 (NDC 65726-251-35) , and a Unit Dose package of 100 (NDC 65726-251-90).

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature] in a tightly closed container. The unit dose packaging should be stored in the carton.

Rx only

April 2004

Reliant
PHARMACEUTICALS LLC

Manufactured for:
Reliant Pharmaceuticals
Liberty Corner, NJ 07938
By:
Eurand America, Inc.
Vandalia, OH 45377

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Reliant Pharmaceuticals
Medical Affairs
110 Allen Road
Liberty Corner, NJ 07938

225R000

Shown in Product Identification Guide, page 331

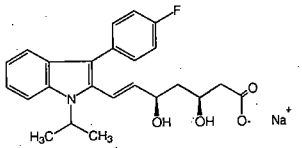
LESCOL®
(fluvastatin sodium)
Capsules
LESCOL® XL
(fluvastatin sodium)
Extended-Release Tablets
Rx only

Prescribing Information

DESCRIPTION

Lescol® (fluvastatin sodium), is a water-soluble cholesterol-lowering agent which acts through the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase.

Fluvastatin sodium is [*R*, S*-(E)]-(±)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1*H*-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid, monosodium salt. The empirical formula of fluvastatin sodium is $C_{24}H_{25}FNO_4 \bullet Na$, its molecular weight is 433.46 and its structural formula is:



$C_{24}H_{25}FNO_4 \bullet Na$ Mol. wt. 433.46

This molecular entity is the first entirely synthetic HMG-CoA reductase inhibitor, and is in part structurally distinct from the fungal derivatives of this therapeutic class.

Fluvastatin sodium is a white to pale yellow, hygroscopic powder soluble in water, ethanol and methanol. Lescol is supplied as capsules containing fluvastatin sodium, equivalent to 20 mg or 40 mg of fluvastatin, for oral administration. Lescol® XL (fluvastatin sodium) is supplied as extended-release tablets containing fluvastatin sodium, equivalent to 80 mg of fluvastatin, for oral administration.

Active Ingredient: fluvastatin sodium

Inactive Ingredients in capsules: gelatin, magnesium stearate, microcrystalline cellulose, pregelatinized starch (corn), red iron oxide, sodium lauryl sulfate, talc, titanium dioxide, yellow iron oxide, and other ingredients.

Capsules may also include: benzyl alcohol, black iron oxide, butylparaben, carboxymethylcellulose sodium, edetate calcium disodium, methylparaben, propylparaben, silicon dioxide and sodium propionate.

Inactive Ingredients in extended-release tablets: microcrystalline cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, potassium bicarbonate, povidone, magnesium stearate, iron oxide yellow, titanium dioxide and polyethylene glycol 8000.

CLINICAL PHARMACOLOGY

A variety of clinical studies have demonstrated that elevated levels of total cholesterol (Total-C), low density lipoprotein cholesterol (LDL-C), apolipoprotein B (a membra
LDL-C) promote human ath
creased levels of HDL-cholester
complex, apolipoprotein A, are
ment of atherosclerosis. Epide
established that cardiovascul
vary directly with the level
inversely with the level of HDI
Like LDL, cholesterol-enriche
teins, including VLDL, IDL and
atherosclerosis. Elevated pla
quently found in a triad with
LDL particles, as well as in as
abolic risk factors for coronary
plasma TG has not consistentl
pendent risk factor for CHD. F
effect of raising HDL or loweri
nd cardiovascular morbidity
ltermined.
patients with hypercholest
lemia, treatment with Lesc
Lescol® XL (fluvastatin sodiu
poliprotein B, and triglyce
crease in HDL-C. Increases i
tients with low HDL-C (<35
consistent effect on either Lp(
Lescol or Lescol XL induced c
including reduction of serum c
mortality has not been determ
Mechanism of Action
Lescol is a competitive inhibi
which is responsible for the
methylglutaryl-coenzyme A (H
precursor of sterols, including
cholesterol biosynthesis reduc
cells, which stimulates the syn
thereby increases the uptake
sult of these biochemical pro
plasma cholesterol concentrati
Pharmacokinetics/Metabolism
Oral Absorption
Fluvastatin is absorbed rapid
ral administration of the caps
ached in less than 1 hour. F
mg dose, the absolute bioa
%). Administration with foo
ent of absorption. At ste
fluvastatin with the evening
crease in C_{max} and more thar
compared to administration 4
No significant differences in e
lipid-lowering effects were obs
istrations. After single or m
fluvastatin exhibits satura
resulting in higher-than-ex
concentrations.
Fluvastatin has two optical
3S and an inactive 3S,5R form
stereo-selective hepatic bindi
during the first pass resultin
levels of the two enantiomers
peak concentration ratio bein
ratio of the active to inactiv
peak is seen and thereafter
with the same half-life. After
sion, bypassing the first-pas
the enantiomers in plasma
oncentration-time profiles.
Fluvastatin administered a
reaches peak concentration in
sting conditions, after a low
ow-fat meal. The mean relat
tablet is approximately 29%
that of the Lescol immediate
nder fasting conditions. Adm
delayed the absorption (T_{max}
vailability of the XL tablet
Lescol XL begins to be absorb
rise rapidly. The maximum co
fat meal is much less than the
a single dose or twice daily dos
Overall variability in the pha
large (42%-64% CV for C_{max} a
er a high fat meal (63%-89
ubject variability in the phar
der fasting conditions (about
o be much smaller as compa
Multiple peaks in plasma flu
been observed after Lescol XL
Distribution
Fluvastatin is 98% bound to p
me of distribution (VD_{ss}) is
parent drug is targeted to th
ites are present systemicall
tions, the protein binding of
warfarin, salicylic acid and gl
Metabolism
Fluvastatin is metabolized i
droxylation of the indole rir
N-dealkylation and beta-oxid
curs. The hydroxy metabolite
tivity, but do not circulate in t
fluvastatin are metabolized i

lipoprotein cholesterol (LDL-C), triglycerides (TG) and apolipoprotein B (a membrane transport complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of HDL-cholesterol (HDL-C) and its transport complex, apolipoprotein A, are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of Total-C and LDL-C and inversely with the level of HDL-C.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, IDL and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

In patients with hypercholesterolemia and mixed dyslipidemia, treatment with Lescol® (fluvastatin sodium) or Lescol® XL (fluvastatin sodium) reduced Total-C, LDL-C, apolipoprotein B, and triglycerides while producing an increase in HDL-C. Increases in HDL-C are greater in patients with low HDL-C (<35 mg/dL). Neither agent had a consistent effect on either Lp(a) or fibrinogen. The effect of Lescol or Lescol XL induced changes in lipoprotein levels, including reduction of serum cholesterol, on cardiovascular mortality has not been determined.

Mechanism of Action

Lescol is a competitive inhibitor of HMG-CoA reductase, which is responsible for the conversion of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate, a precursor of sterols, including cholesterol. The inhibition of cholesterol biosynthesis reduces the cholesterol in hepatic cells, which stimulates the synthesis of LDL receptors and thereby increases the uptake of LDL particles. The end result of these biochemical processes is a reduction of the plasma cholesterol concentration.

Pharmacokinetics/Metabolism

Oral Absorption

Fluvastatin is absorbed rapidly and completely following oral administration of the capsule, with peak concentrations reached in less than 1 hour. Following administration of a 10 mg dose, the absolute bioavailability is 24% (range 9%-36%). Administration with food reduces the rate but not the *extent* of absorption. At steady-state, administration of fluvastatin with the evening meal results in a two-fold decrease in C_{max} and more than two-fold increase in t_{max} as compared to administration 4 hours after the evening meal. No significant differences in extent of absorption or in the lipid-lowering effects were observed between the two administrations. After single or multiple doses above 20 mg, fluvastatin exhibits saturable first-pass metabolism resulting in higher-than-expected plasma fluvastatin concentrations.

Fluvastatin has two optical enantiomers, an active 3R, 5S and an inactive 3S,5R form. In vivo studies showed that stereo-selective hepatic binding of the active form occurs during the first pass resulting in a difference in the peak levels of the two enantiomers, with the active to inactive peak concentration ratio being about 0.7. The approximate ratio of the active to inactive approaches unity after the peak is seen and thereafter the two enantiomers decline with the same half-life. After an intravenous administration, bypassing the first-pass metabolism, the ratios of the enantiomers in plasma were similar throughout the concentration-time profiles.

Fluvastatin administered as Lescol XL 80 mg tablets reaches peak concentration in approximately 3 hours under fasting conditions, after a low-fat meal, or 2.5 hours after a low-fat meal. The mean relative bioavailability of the XL tablet is approximately 29% (range: 9%-66%) compared to that of the Lescol immediate release capsule administered under fasting conditions. Administration of a high fat meal delayed the absorption (T_{max}: 6H) and increased the bioavailability of the XL tablet by approximately 50%. Once Lescol XL begins to be absorbed, fluvastatin concentrations rise rapidly. The maximum concentration seen after a high fat meal is much less than the peak concentration following a single dose or twice daily dose of the 40 mg Lescol capsule. Overall variability in the pharmacokinetics of Lescol XL is large (42%-64% CV for C_{max} and AUC), and especially so after a high fat meal (63%-89% for C_{max} and AUC). Intra-subject variability in the pharmacokinetics of Lescol XL under fasting conditions (about 25% for C_{max} and AUC) tends to be much smaller as compared to the overall variability. Multiple peaks in plasma fluvastatin concentrations have been observed after Lescol XL administration.

Distribution

Fluvastatin is 98% bound to plasma proteins. The mean volume of distribution (VD_{ss}) is estimated at 0.35 L/kg. The parent drug is targeted to the liver and no active metabolites are present systemically. At therapeutic concentrations, the protein binding of fluvastatin is not affected by warfarin, salicylic acid and glyburide.

Metabolism

Fluvastatin is metabolized in the liver, primarily via hydroxylation of the indole ring at the 5- and 6-positions. N-dealkylation and beta-oxidation of the side-chain also occurs. The hydroxy metabolites have some pharmacologic activity, but do not circulate in the blood. Both enantiomers of fluvastatin are metabolized in a similar manner.

Table 1
Single-Dose and Steady-State Pharmacokinetic Parameters

	C_{max} (ng/mL) mean ± SD (range)	AUC (ng·h/mL) mean ± SD (range)	t_{max} (hr) mean ± SD (range)	CL/F (L/hr) mean ± SD (range)	$t_{1/2}$ (hr) mean ± SD (range)
Capsules					
20 mg single dose (n=17)	166±106 (48.9-517)	207±65 (111-288)	0.9±0.4 (0.5-2.0)	107±38.1 (69.5-181)	2.5±1.7 (0.5-6.6)
20 mg twice daily (n=17)	200±86 (71.8-366)	275±111 (91.6-467)	1.2±0.9 (0.5-4.0)	87.8±45 (42.8-218)	2.8±1.7 (0.9-6.0)
40 mg single dose (n=16)	273±189 (72.8-812)	456±259 (207-1221)	1.2±0.7 (0.75-3.0)	108±44.7 (32.8-193)	2.7±1.3 (0.8-5.9)
40 mg twice daily (n=16)	432±236 (119-990)	697±275 (359-1559)	1.2±0.6 (0.5-2.5)	64.2±21.1 (25.7-111)	2.7±1.3 (0.7-5.0)
Extended-Release Tablets 80 mg single dose (n=24)					
80 mg single dose, fasting (n=24)	126±53 (37-242)	579±341 (144-1760)	3.2±2.6 (1-12)		
80 mg single dose, fed-state high fat meal (n=24)	183±163 (21-733)	861±632 (199-3132)	6 (2-24)		
Extended-Release Tablets 80 mg following 7 days dosing (steady-state) (n=11)					
80 mg once daily, fasting (n=11)	102±42 (43.9-181)	630±326 (247-1406)	2.6±0.91 (1.5-4)		

Table 2
Median Percent Change in Lipid Parameters from Baseline to Week 24 Endpoint
All Placebo-Controlled Studies (Lescol®) and Active Controlled Trials (Lescol® XL)

	Total Chol.		TG		LDL		Apo B		HDL	
Dose	N	% Δ	N	% Δ	N	% Δ	N	% Δ	N	% Δ
All Patients										
Lescol 20 mg[1]	747	-17	747	-12	747	-22	114	-19	747	+3
Lescol 40 mg[1]	748	-19	748	-14	748	-25	125	-18	748	+4
Lescol 40 mg twice daily[1]	257	-27	257	-18	257	-36	232	-28	257	+6
Lescol XL 80 mg[2]	750	-25	750	-19	748	-35	745	-27	750	+7
Baseline TG ≥200 mg/dL										
Lescol 20 mg[1]	148	-16	148	-17	148	-22	23	-19	148	+6
Lescol 40 mg[1]	179	-18	179	-20	179	-24	47	-18	179	+7
Lescol 40 mg twice daily[1]	76	-27	76	-23	76	-35	69	-28	76	+9
Lescol XL 80 mg[2]	239	-25	239	-25	237	-33	235	-27	239	+11

[1]Data for Lescol from 12 placebo controlled trials
[2]Data for Lescol XL 80 mg tablet from three 24 week controlled trials

In vitro studies demonstrated that fluvastatin undergoes oxidative metabolism, predominantly via 2C9 isozyme systems (75%). Other isozymes that contribute to fluvastatin metabolism are 2C8 (~5%) and 3A4 (~20%). *(See PRECAUTIONS: Drug Interactions Section).*

Elimination

Fluvastatin is primarily (about 90%) eliminated in the feces as metabolites, with less than 2% present as unchanged drug. Urinary recovery is about 5%. After a radiolabeled dose of fluvastatin, the clearance was 0.8 L/h/kg. Following multiple oral doses of radiolabeled compound, there was no accumulation of fluvastatin; however, there was a 2.3 fold accumulation of total radioactivity.

Steady-state plasma concentrations show no evidence of accumulation of fluvastatin following immediate release capsule administration of up to 80 mg daily, as evidenced by a beta-elimination half-life of less than 3 hours. However, under conditions of maximum rate of absorption (i.e., fasting) systemic exposure to fluvastatin is increased 33% to 53% compared to a single 20 mg or 40 mg dose of the immediate release capsule. Following once daily administration of the 80 mg Lescol XL tablet for 7 days, systemic exposure to fluvastatin is increased (20%-30%) compared to a single dose of the 80 mg Lescol XL tablet. Terminal half-life of Lescol XL was about 9 hours as a result of the slow-release formulation.

Single-dose and steady-state pharmacokinetic parameters in 33 subjects with hypercholesterolemia for the capsules and in 35 healthy subjects for the extended-release tablets are summarized below:

[See table 1 above]

Special Populations

Renal Insufficiency: No significant (<6%) renal excretion of fluvastatin occurs in humans.

Hepatic Insufficiency: Fluvastatin is subject to saturable first-pass metabolism/sequestration by the liver and is eliminated primarily via the biliary route. Therefore, the potential exists for drug accumulation in patients with hepatic insufficiency. Caution should therefore be exercised when fluvastatin sodium is administered to patients with a history of liver disease or heavy alcohol ingestion *(see WARNINGS).*

Fluvastatin AUC and C_{max} values increased by about 2.5 fold in hepatic insufficiency patients. This result was attributed to the decreased presystemic metabolism due to hepatic dysfunction. The enantiomer ratios of the two isomers of fluvastatin in hepatic insufficiency patients were comparable to those observed in healthy subjects.

Age: Plasma levels of fluvastatin are not affected by age.

Gender: Women tend to have slightly higher (but statistically insignificant) fluvastatin concentrations than men for the immediate release capsule. This is most likely due to body weight differences, as adjusting for body weight decreases the magnitude of the differences seen. For Lescol XL, there are 67% and 77% increases in systemic availability for women over men under fasted and high fat meal conditions.

Pediatric: No data are available. Fluvastatin is not indicated for use in the pediatric population.

CLINICAL STUDIES

Hypercholesterolemia (heterozygous familial and non familial) and Mixed Dyslipidemia

In 12 placebo-controlled studies in patients with Type IIa or IIb hyperlipoproteinemia, Lescol® (fluvastatin sodium) alone was administered to 1621 patients in daily dose regimens of 20 mg, 40 mg, and 80 mg (40 mg twice daily) for at least 6 weeks duration. After 24 weeks of treatment, daily doses of 20 mg, 40 mg, and 80 mg (40 mg twice daily) resulted in median LDL-C reductions of 22% (n=747), 25% (n=748) and 36% (n=257), respectively. Lescol treatment produced dose-related reductions in Apo B and in triglycerides and increases in HDL-C. The median (25th, 75th percentile) percent changes from baseline in HDL-C after 12 weeks of treatment with Lescol at daily doses of 20 mg, 40 mg and 80 mg (40 mg twice daily) were +2 (-4,+10), +5 (-2,+12), and +4 (-3,+12), respectively. In a subgroup of patients with primary mixed dyslipidemia, defined as baseline TG levels ≥200 mg/dL, treatment with Lescol also produced significant decreases in Total-C, LDL-C, TG and Apo B and variable increases in HDL-C. The median (25th 75th percentile) percent changes from baseline in HDL-C after 12 weeks of treatment with Lescol at daily doses of 20 mg, 40 mg and 80 mg (40 mg twice daily) in this population were +4 (-2,+12), +8 (+1,+15), and +4 (-3,+13), respectively.

In a long-term open-label free titration study, after 96 weeks LDL-C decreases of 25% (20 mg, n=68), 31% (40 mg, n=298) and 34% (80 mg, n=209) were seen. No consistent effect on Lp(a) was observed.

Lescol® XL (fluvastatin sodium) Extended-Release Tablets have been studied in five controlled studies of patients with Type IIa or IIb hyperlipoproteinemia. Lescol XL was administered to over 900 patients in trials from 4 to 26 weeks in duration. In the three largest of these studies, Lescol XL given as a single daily dose of 80 mg significantly reduced Total-C, LDL-C, TG and Apo B. Therapeutic response is well established within two weeks, and a maximum response is achieved within four weeks. After four weeks of therapy, the median decrease in LDL-C was 38% and at week 24 endpoint the median LDL-C decrease was 35%. Significant in-

Continued on next page

Lescol/Lescol XL—Cont.

creases in HDL-C were also observed. The median (25th and 75th percentile) percent changes from baseline in HDL-C for Lescol XL were +7(+0,+15) after 24 weeks of treatment.

[See table 2 on previous page]

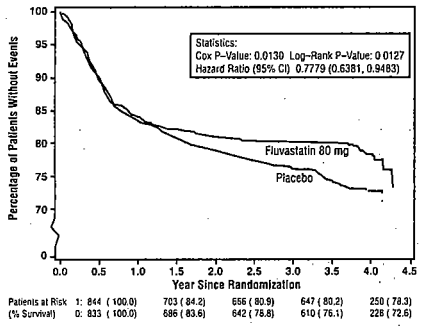
In patients with primary mixed dyslipidemia (Fredrickson Type IIb) as defined by baseline plasma triglycerides levels ≥200 mg/dL, Lescol XL 80 mg produced a median reduction in triglycerides of 25%. In these patients, Lescol XL 80 mg produced median (25th and 75th percentile) percent change from baseline in HDL-C of +11(+3,+20). Significant decreases in Total-C, LDL-C, and Apo B were also achieved. In these studies, patients with triglycerides >400 mg/dL were excluded.

Reduction in the Risk of Recurrent Cardiac Events

In the Lescol Intervention Prevention Study, the effect of Lescol 40 mg administered twice daily on the risk of recurrent cardiac events (time to first occurrence of cardiac death, nonfatal myocardial infarction, or revascularization) was assessed in 1677 patients with coronary heart disease who had undergone a percutaneous coronary intervention (PCI) procedure (mean time from PCI to randomization=3 days). In this multicenter, randomized, double-blind, placebo-controlled study, patients were treated with dietary/lifestyle counseling and either Lescol 40 mg (n=844) or placebo (n=833) given twice daily for a median of 3.9 years. The study population was 84% male, 98% Caucasian, with 37% >65 years of age. At baseline patients had total cholesterol between 100 and 367 mg/dL (mean 201 mg/dL), LDL-C between 42 and 243 mg/dL (mean 132 mg/dL), triglycerides between 15 and 270 mg/dL (mean 70 mg/dL) and HDL-C between 8 and 174 mg/dL (mean 39 mg/dL).

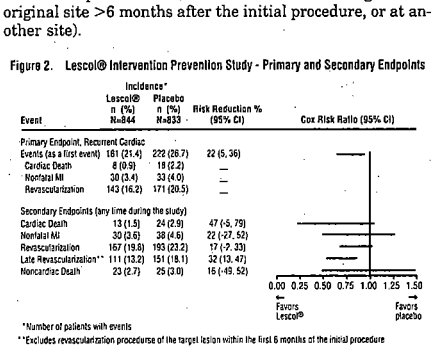
Lescol significantly reduced the risk of recurrent cardiac events (Figure 1) by 22% (p=0.013, 181 patients in the Lescol group vs. 222 patients in the placebo group). Revascularization procedures comprised the majority of the initial recurrent cardiac events (143 revascularization procedures in the Lescol group and 171 in the placebo group). Consistent trends in risk reduction were observed in patients >65 years of age.

Figure 1. Primary Endpoint - Recurrent Cardiac Events (Cardiac Death, Nonfatal MI or Revascularization Procedure) (ITT Population)



Outcome data for the Lescol Intervention Prevention Study are shown in Figure 2. After exclusion of revascularization procedures (CABG and repeat PCI) occurring within the first 6 months of the initial procedure involving the originally instrumented site, treatment with Lescol was associated with a 32% (p=0.002) reduction in risk of late revascularization procedures (CABG or PCI occurring at the original site >6 months after the initial procedure, or at another site).

Figure 2. Lescol® Intervention Prevention Study - Primary and Secondary Endpoints



*Number of patients with events

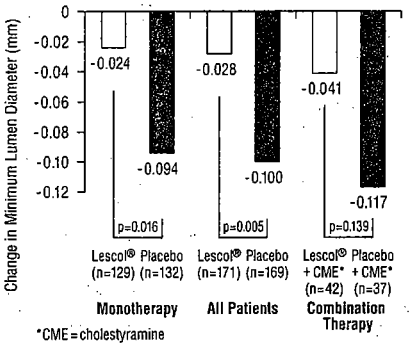
**Excludes revascularization procedures of the target lesion within the first 6 months of the initial procedure

Atherosclerosis

In the Lipoprotein and Coronary Atherosclerosis Study (LCAS), the effect of Lescol therapy on coronary atherosclerosis was assessed by quantitative coronary angiography (QCA) in patients with coronary artery disease and mild to moderate hypercholesterolemia (baseline LDL-C range 115-190 mg/dL). In this randomized double-blind, placebo controlled trial, 429 patients were treated with conventional measures (Step 1 AHA Diet) and either Lescol 40 mg/day or placebo. In order to provide treatment to patients receiving placebo with LDL-C levels ≥160 mg/dL at baseline, adjunctive therapy with cholestyramine was added after week 12 to all patients in the study with baseline LDL-C values of ≥160 mg/dL. These baseline levels were present in 25% of the study population. Quantitative coronary angiograms were evaluated at baseline and 2.5 years in 340 (79%) angiographic evaluable patients.

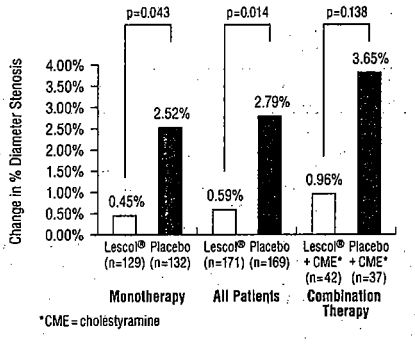
Lescol significantly slowed the progression of coronary atherosclerosis. Compared to placebo, Lescol significantly slowed the progression of lesions as measured by within-patient per-lesion change in minimum lumen diameter (MLD), the primary endpoint (see Figure 3 below), percent diameter stenosis (Figure 4), and the formation of new lesions (13% of all fluvastatin patients versus 22% of all placebo patients). Additionally, a significant difference in favor of Lescol was found between all fluvastatin and all placebo patients in the distribution among the three categories of definite progression, definite regression, and mixed or no change. Beneficial angiographic results (change in MLD) were independent of patients' gender and consistent across a range of baseline LDL-C levels.

Figure 3
Change in Minimum Lumen Diameter (mm)



*CME = cholestyramine

Figure 4
Change in % Diameter Stenosis



*CME = cholestyramine

INDICATIONS AND USAGE

Therapy with lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol (see National Cholesterol Education Program (NCEP) Treatment Guidelines, below).

Hypercholesterolemia (heterozygous familial and non familial) and Mixed Dyslipidemia

Lescol® (fluvastatin sodium) and Lescol® XL (fluvastatin sodium) are indicated to reduce elevated total cholesterol (Total-C), LDL-C, TG and Apo B levels, and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Type IIa and IIb) whose response to dietary restriction of saturated fat and cholesterol and other nonpharmacological measures has not been adequate.

Secondary Prevention of Coronary Events

In patients with coronary heart disease, Lescol and Lescol XL are indicated to reduce the risk of undergoing coronary revascularization procedures.

Atherosclerosis

Lescol and Lescol XL are also indicated to slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower total and LDL cholesterol to target levels.

Therapy with lipid-altering agents should be considered only after secondary causes for hyperlipidemia such as poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other medication, or alcoholism, have been excluded. Prior to initiation of fluvastatin sodium, a lipid profile should be performed to measure Total-C, HDL-C and TG. For patients with TG <400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation:

LDL-C = Total-C - HDL-C - 1/5 TG

For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In many hypertriglyceridemic patients LDL-C may be low or normal despite elevated Total-C. In such cases, Lescol is not indicated.

Lipid determinations should be performed at intervals of no less than 4 weeks and dosage adjusted according to the patient's response to therapy.

The National Cholesterol Education Program (NCEP) Treatment Guidelines are summarized below:

[See table 3 at top of next page]

After the LDL-C goal has been achieved, if the TG is still ≥200 mg/dL, non-HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

At the time of hospitalization for an acute coronary event, consideration can be given to initiating drug therapy at discharge if the LDL-C level is ≥130 mg/dL (NCEP-ATP II).

Since the goal of treatment is to lower LDL-C, the NCEP recommends that the LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should the Total-C be used to monitor therapy.

[See table 4 at top of next page]

Neither Lescol nor Lescol XL have been studied in conditions where the major abnormality is elevation of chylomicrons, VLDL, or IDL (i.e., hyperlipoproteinemia Types I, III, IV, or V).

CONTRAINDICATIONS

Hypersensitivity to any component of this medication. Lescol® (fluvastatin sodium) and Lescol® XL (fluvastatin sodium) are contraindicated in patients with active liver disease or unexplained, persistent elevations in serum transaminases *(see WARNINGS)*.

Pregnancy and Lactation

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Fluvastatin sodium should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes

Biochemical abnormalities of liver function have been associated with HMG-CoA reductase inhibitors and other lipid-lowering agents. Approximately 1.1% of patients treated with Lescol® (fluvastatin sodium) capsules in worldwide trials developed dose-related, persistent elevations of transaminase levels to more than 3 times the upper limit of normal. Fourteen of these patients (0.6%) were discontinued from therapy. In all clinical trials, a total of 33/2969 patients (1.1%) had persistent transaminase elevations with an average fluvastatin exposure of approximately 71.2 weeks; 19 of these patients (0.6%) were discontinued. The majority of patients with these abnormal biochemical findings were asymptomatic.

In a pooled analysis of all placebo-controlled studies in which Lescol capsules were used, persistent transaminase elevations (>3 times the upper limit of normal [ULN] on two consecutive weekly measurements) occurred in 0.2%, 1.5%, and 2.7% of patients treated with 20, 40, and 80 mg (titrated to 40 mg twice daily) Lescol capsules, respectively. Ninety-one percent of the cases of persistent liver function test abnormalities (20 of 22 patients) occurred within 12 weeks of therapy and in all patients with persistent liver function test abnormalities there was an abnormal liver function test present at baseline or by week 8.

In the pooled analysis of the 24-week controlled trials, persistent transaminase elevation occurred in 1.9%, 1.8% and 4.9% of patients treated with Lescol® XL (fluvastatin sodium) 80 mg, Lescol 40 mg and Lescol 40 mg twice daily, respectively. In 13 of 16 patients treated with Lescol XL the abnormality occurred within 12 weeks of initiation of treatment with Lescol XL 80 mg.

It is recommended that liver function tests be performed before the initiation of therapy and at 12 weeks following initiation of treatment or elevation in dose. Patients who develop transaminase elevations or signs and symptoms of liver disease should be monitored to confirm the finding and should be followed thereafter with frequent liver function tests until the levels return to normal. Should an increase in AST or ALT of three times the upper limit of normal or greater persist (found on two consecutive occasions) withdrawal of fluvastatin sodium therapy is recommended.

Active liver disease or unexplained transaminase elevations are contraindications to the use of Lescol and Lescol XL *(see CONTRAINDICATIONS)*. Caution should be exercised when fluvastatin sodium is administered to patients with a history of liver disease or heavy alcohol ingestion *(see CLINICAL PHARMACOLOGY: Pharmacokinetics / Metabolism)*. Such patients should be closely monitored.

Skeletal Muscle

Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with fluvastatin and with other drugs in this class. Myopathy, defined as muscle ach-

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PRECAUTIONS

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Drug Interactions

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ing or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal, has been reported.

Myopathy should be considered in any patients with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Fluvastatin sodium therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Fluvastatin sodium therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.

The risk of myopathy and or rhabdomyolysis during treatment with HMG-CoA reductase inhibitors has been reported to be increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. Myopathy was not observed in a clinical trial in 74 patients involving patients who were treated with fluvastatin sodium together with niacin.

Uncomplicated myalgia has been observed infrequently in patients treated with Lescol at rates indistinguishable from placebo.

The use of fibrates alone may occasionally be associated with myopathy. The combined use of HMG-CoA reductase inhibitors and fibrates should generally be avoided.

PRECAUTIONS

General

Before instituting therapy with Lescol® (fluvastatin sodium) or Lescol® XL (fluvastatin sodium), an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems *(see INDICATIONS AND USAGE)*.

The HMG-CoA reductase inhibitors may cause elevation of creatine phosphokinase and transaminase levels *(see WARNINGS and ADVERSE REACTIONS)*. This should be considered in the differential diagnosis of chest pain in a patient on therapy with fluvastatin sodium.

Homozygous Familial Hypercholesterolemia

HMG-CoA reductase inhibitors are reported to be less effective in patients with rare homozygous familial hypercholesterolemia, possibly because these patients have few functional LDL receptors.

Information for Patients

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Women should be informed that if they become pregnant while receiving Lescol or Lescol XL the drug should be discontinued immediately to avoid possible harmful effects on a developing fetus from a relative deficit of cholesterol and biological products derived from cholesterol. In addition, Lescol or Lescol XL should not be taken during nursing. *(See CONTRAINDICATIONS.)*

Drug Interactions

The below listed drug interaction information is derived from studies using immediate release fluvastatin. Similar studies have not been conducted using the Lescol XL tablet.

Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin (See WARNINGS: Skeletal Muscle).

In vitro data indicate that fluvastatin metabolism involves multiple Cytochrome P450 (CYP) isozymes. CYP2C9 isoenzyme is primarily involved in the metabolism of fluvastatin (~75%), while CYP2C8 and CYP3A4 isoenzymes are involved to a much less extent, i.e. ~5% and ~20%, respectively. If one pathway is inhibited in the elimination process of fluvastatin other pathways may compensate.

In vivo drug interaction studies with CYP3A4 inhibitors/substrates such as cyclosporine, erythromycin, and itraconazole result in minimal changes in the pharmacokinetics of fluvastatin, confirming less involvement of CYP3A4 isozyme. Concomitant administration of fluvastatin and phenytoin increased the levels of phenytoin and fluvastatin, suggesting predominant involvement of CYP2C9 in fluvastatin metabolism.

Niacin/Propranolol: Concomitant administration of immediate release fluvastatin sodium with niacin or propranolol has no effect on the bioavailability of fluvastatin sodium.

Cholestyramine: Administration of immediate release fluvastatin sodium concomitantly with, or up to 4 hours after cholestyramine, results in fluvastatin decreases of more than 50% for AUC and 50%-80% for C_{max}. However, administration of immediate release fluvastatin sodium 4 hours after cholestyramine resulted in a clinically significant additive effect compared with that achieved with either component drug.

Cyclosporine: Plasma cyclosporine levels remain unchanged when fluvastatin (20 mg daily) was administered concurrently in renal transplant recipients on stable cyclosporine regimens. Fluvastatin AUC increased 1.9 fold, and C_{max} increased 1.3 fold compared to historical controls.

Digoxin: In a crossover study involving 18 patients chronically receiving digoxin, a single 40 mg dose of immediate release fluvastatin had no effect on digoxin AUC, but had an 11% increase in digoxin C_{max} and small increase in digoxin urinary clearance.

Table 3
NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD† or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional)††
2+ Risk factors (10-year risk ≤20%)	<130	≥130	10-year risk 10%-20%: ≥130 10-year risk <10%: ≥160
0–1 Risk factor†††	<160	≥160	≥190 (160–189: LDL-lowering drug optional)

†CHD, coronary heart disease
††Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g. nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.
†††Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

Table 4
Classification of Hyperlipoproteinemias

Type	Lipoproteins Elevated	Lipid Elevations: Major	Lipid Elevations: Minor
I (rare)	Chylomicrons	TG	↑ → C
IIa	LDL	C	–
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C/TG	–
IV	VLDL	TG	↑ → C
V (rare)	Chylomicrons, VLDL	TG	↑ → C

C = cholesterol, TG = triglycerides, LDL = low density lipoprotein, VLDL = very low density lipoprotein, IDL = intermediate density lipoprotein

Erythromycin: Erythromycin (500 mg, single dose) did not affect steady-state plasma levels of fluvastatin (40 mg daily).

Itraconazole: Concomitant administration of fluvastatin (40 mg) and itraconazole (100 mg daily × 4 days) does not affect plasma itraconazole or fluvastatin levels.

Gemfibrozil: There is no change in either fluvastatin (20 mg twice daily) or gemfibrozil (600 mg twice daily) plasma levels when these drugs are co-administered.

Phenytoin: Single-morning dose administration of phenytoin (300 mg extended release) increased mean steady-state fluvastatin (40 mg) C_{max} by 27% and AUC by 40% whereas fluvastatin increased the mean phenytoin C_{max} by 5% and AUC by 20%. Patients on phenytoin should continue to be monitored appropriately when fluvastatin therapy is initiated or when the fluvastatin dosage is changed.

Diclofenac: Concurrent administration of fluvastatin (40 mg) increased the mean C_{max} and AUC of diclofenac by 60% and 25% respectively.

Tolbutamide: In healthy volunteers, concurrent administration of either single or multiple daily doses of fluvastatin sodium (40 mg) with tolbutamide (1 g) did not affect the plasma levels of either drug to a clinically significant extent.

Glibenclamide (Glyburide): In glibenclamide-treated NIDDM patients (n=32), administration of fluvastatin (40 mg twice daily for 14 days) increased the mean C_{max}, AUC, and $t_{1/2}$ of glibenclamide approximately 50%, 69% and 121%, respectively. Glibenclamide (5-20 mg daily) increased the mean C_{max} and AUC of fluvastatin by 44% and 51%, respectively. In this study there were no changes in glucose, insulin and C-peptide levels. However, patients on concomitant therapy with glibenclamide (glyburide) and fluvastatin should continue to be monitored appropriately when their fluvastatin dose is increased to 40 mg twice daily.

Losartan: Concomitant administration of fluvastatin with losartan has no effect on the bioavailability of either losartan or its active metabolite.

Cimetidine/Ranitidine/Omeprazole: Concomitant administration of immediate release fluvastatin sodium with cimetidine, ranitidine and omeprazole results in a significant increase in the fluvastatin C_{max} (43%, 70% and 50%, respectively) and AUC (24%-33%), with an 18%-23% decrease in plasma clearance.

Rifampicin: Administration of immediate release fluvastatin sodium to subjects pretreated with rifampicin results in significant reduction in C_{max} (59%) and AUC (51%), with a large increase (95%) in plasma clearance.

Warfarin: In vitro protein binding studies demonstrated no interaction at therapeutic concentrations. Concomitant administration of a single dose of warfarin (30 mg) in young healthy males receiving immediate release fluvastatin sodium (40 mg/day × 8 days) resulted in no elevation of racemic warfarin concentration. There was also no effect on prothrombin complex activity when compared to concomitant administration of placebo and warfarin. However, bleeding and/or increased prothrombin times have been reported in patients taking coumarin anticoagulants concomitantly with other HMG-CoA reductase inhibitors. Therefore, patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when fluvastatin sodium is initiated or the dosage of fluvastatin sodium is changed.

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production.

Fluvastatin exhibited no effect upon non-stimulated cortisol levels and demonstrated no effect upon thyroid metabolism as assessed by TSH. Small declines in total testosterone have been noted in treated groups, but no commensurate elevation in LH occurred, suggesting that the observation was not due to a direct effect upon testosterone production. No effect upon FSH in males was noted. Due to the limited number of premenopausal females studied to date, no conclusions regarding the effect of fluvastatin upon female sex hormones may be made.

Two clinical studies in patients receiving fluvastatin at doses up to 80 mg daily for periods of 24 to 28 weeks demonstrated no effect of treatment upon the adrenal response to ACTH stimulation. A clinical study evaluated the effect of fluvastatin at doses up to 80 mg daily for 28 weeks upon the gonadal response to HCG stimulation. Although the mean total testosterone response was significantly reduced ($p<0.05$) relative to baseline in the 80 mg group, it was not significant in comparison to the changes noted in groups receiving either 40 mg of fluvastatin or placebo.

Patients treated with fluvastatin sodium who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients receiving other drugs (e.g., ketoconazole, spironolactone, or cimetidine) that may decrease the levels of endogenous steroid hormones.

CNS Toxicity

CNS effects, as evidenced by decreased activity, ataxia, loss of righting reflex, and ptosis were seen in the following animal studies: the 18-month mouse carcinogenicity study at 50 mg/kg/day, the 6-month dog study at 36 mg/kg/day, the 6-month hamster study at 40 mg/kg/day, and in acute, high-dose studies in rats and hamsters (50 mg/kg), rabbits (300 mg/kg) and mice (1500 mg/kg). CNS toxicity in the acute high-dose studies was characterized (in mice) by conspicuous vacuolation in the ventral white columns of the spinal cord at a dose of 5000 mg/kg and (in rat) by edema with separation of myelinated fibers of the ventral spinal tracts and sciatic nerve at a dose of 1500 mg/kg. CNS toxicity, characterized by periaxonal vacuolation, was observed in the medulla of dogs that died after treatment for 5 weeks with 48 mg/kg/day; this finding was not observed in the remaining dogs when the dose level was lowered to 36 mg/kg/day. CNS vascular lesions, characterized by perivascular

Continued on next page

Lescol/Lescol XL—Cont.

hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. No CNS lesions have been observed after chronic treatment for up to 2 years with fluvastatin in the mouse (at doses up to 350 mg/kg/day), rat (up to 24 mg/kg/day), or dog (up to 16 mg/kg/day).
Prominent bilateral posterior Y suture lines in the ocular lens were seen in dogs after treatment with 1, 8, and 16 mg/kg/day for 2 years.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 2-year study was performed in rats at dose levels of 6, 9, and 18-24 (escalated after 1 year) mg/kg/day. These treatment levels represented plasma drug levels of approximately 9, 13, and 26-35 times the mean human plasma drug concentration after a 40 mg oral dose. A low incidence of forestomach squamous papillomas and 1 carcinoma of the forestomach at the 24 mg/kg/day dose level was considered to reflect the prolonged hyperplasia induced by direct contact exposure to fluvastatin sodium rather than to a systemic effect of the drug. In addition, an increased incidence of thyroid follicular cell adenomas and carcinomas was recorded for males treated with 18-24 mg/kg/day. The increased incidence of thyroid follicular cell neoplasm in male rats with fluvastatin sodium appears to be consistent with findings from other HMG-CoA reductase inhibitors. In contrast to other HMG-CoA reductase inhibitors, no hepatic adenomas or carcinomas were observed.
The carcinogenicity study conducted in mice at dose levels of 0.3, 15 and 30 mg/kg/day revealed, as in rats, a statistically significant increase in forestomach squamous cell papillomas in males and females at 30 mg/kg/day and in females at 15 mg/kg/day. These treatment levels represented plasma drug levels of approximately 0.05, 2, and 7 times the mean human plasma drug concentration after a 40 mg oral dose.
No evidence of mutagenicity was observed in vitro, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests using mutant strains of *Salmonella typhimurium* or *Escherichia coli;* malignant transformation assay in BALB/3T3 cells; unscheduled DNA synthesis in rat primary hepatocytes; chromosomal aberrations in V79 Chinese Hamster cells; HGPRT V79 Chinese Hamster cells. In addition, there was no evidence of mutagenicity in vivo in either a rat or mouse micronucleus test.
In a study in rats at dose levels for females of 0.6, 2 and 6 mg/kg/day and at dose levels for males of 2, 10 and 20 mg/kg/day, fluvastatin sodium had no adverse effects on the fertility or reproductive performance.
Seminal vesicles and testes were small in hamsters treated for 3 months at 20 mg/kg/day (approximately three times the 40 milligram human daily dose based on surface area, mg/m^2). There was tubular degeneration and aspermatogenesis in testes as well as vesiculitis of seminal vesicles. Vesiculitis of seminal vesicles and edema of the testes were also seen in rats treated for 2 years at 18 mg/kg/day (approximately 4 times the human C_{max} achieved with a 40 milligram daily dose).

Pregnancy

Pregnancy Category X

See CONTRAINDICATIONS.
Fluvastatin sodium produced delays in skeletal development in rats at doses of 12 mg/kg/day and in rabbits at doses of 10 mg/kg/day. Malaligned thoracic vertebrae were seen in rats at 36 mg/kg, a dose that produced maternal toxicity. These doses resulted in 2 times (rat at 12 mg/kg) or 5 times (rabbit at 10 mg/kg) the 40 mg human exposure based on mg/m^2 surface area. A study in which female rats were dosed during the third trimester at 12 and 24 mg/kg/day resulted in maternal mortality at or near term and postpartum. In addition, fetal and neonatal lethality were apparent. No effects on the dam or fetus occurred at 2 mg/kg/day. A second study at levels of 2, 6, 12 and 24 mg/kg/day confirmed the findings in the first study with neonatal mortality beginning at 6 mg/kg. A modified Segment III study was performed at dose levels of 12 or 24 mg/kg/day with or without the presence of concurrent supplementation with mevalonic acid, a product of HMG-CoA reductase which is essential for cholesterol biosynthesis. The concurrent administration of mevalonic acid completely prevented the maternal and neonatal mortality but did not prevent low body weights in pups at 24 mg/kg on days 0 and 7 postpartum. Therefore, the maternal and neonatal lethality observed with fluvastatin sodium reflect its exaggerated pharmacologic effect during pregnancy. There are no data with fluvastatin sodium in pregnant women. However, rare reports of congenital anomalies have been received following intrauterine exposure to other HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took another HMG-CoA reductase inhibitor with dextroamphetamine sulfate during the first trimester of pregnancy. **Lescol or Lescol XL should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If a woman becomes pregnant while taking Lescol or Lescol XL, the drug should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers

Based on preclinical data, drug is present in breast milk in a 2:1 ratio (milk:plasma). Because of the potential for serious adverse reactions in nursing infants, nursing women should not take Lescol or Lescol XL *(see CONTRAINDICATIONS).*

Pediatric Use

Safety and effectiveness in individuals less than 18 years old have not been established. Treatment in patients less than 18 years of age is not recommended at this time.

Geriatric Use

The effect of age on the pharmacokinetics of immediate release fluvastatin sodium was evaluated. Results indicate that for the general patient population plasma concentrations of fluvastatin sodium do not vary as a function of age. *(See also CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism.)* Elderly patients (≥65 years of age) demonstrated a greater treatment response in respect to LDL-C, Total-C and LDL/HDL ratio than patients <65 years of age.

ADVERSE REACTIONS

In all clinical studies of Lescol® (fluvastatin sodium), 1.0% (32/2969) of fluvastatin-treated patients were discontinued due to adverse experiences attributed to study drug (mean exposure approximately 16 months ranging in duration from 1 to >36 months). This results in an exposure adjusted rate of 0.8% (32/4051) per patient year in fluvastatin patients in controlled studies compared to an incidence of 1.1% (4/355) in placebo patients. Adverse reactions have usually been of mild to moderate severity.
In controlled clinical studies, 3.9% (36/912) of patients treated with Lescol® XL (fluvastatin sodium) 80 mg discontinued due to adverse events (causality not determined).
Clinically relevant adverse experiences occurring in the Lescol and Lescol XL controlled studies with a frequency >2%, regardless of causality, include the following:

Table 5
Clinically Relevant Adverse Experiences Occurring in >2% Patients in Lescol® and Lescol XL® Controlled Studies

Adverse Event	Lescol®[1] (%) (N=2326)	Placebo[1] (%) (N=960)	Lescol® XL[2] (%) (N=912)
Musculoskeletal			
Myalgia	5.0	4.5	3.8
Arthritis	2.1	2.0	1.3
Arthropathy	NA	NA	3.2
Respiratory			
Sinusitis	2.6	1.9	3.5
Bronchitis	1.8	1.0	2.6
Gastrointestinal			
Dyspepsia	7.9	3.2	3.5
Diarrhea	4.9	4.2	3.3
Abdominal Pain	4.9	3.8	3.7
Nausea	3.2	2.0	2.5
Flatulence	2.6	2.5	1.4
Psychiatric Disorders			
Insomnia	2.7	1.4	0.8
Genitourinary			
Urinary Tract Infection	1.6	1.1	2.7
Miscellaneous			
Headache	8.9	7.8	4.7
Influenza-Like Symptoms	5.1	5.7	7.1
Accidental Trauma	5.1	4.8	4.2
Fatigue	2.7	2.3	1.6
Allergy	2.3	2.2	1.0

[1] Controlled trials with Lescol Capsules (20 and 40 mg daily and 40 mg twice daily)
[2] Controlled trials with Lescol XL 80 mg Tablets

The following effects have been reported with drugs in this class. Not all the effects listed below have necessarily been associated with fluvastatin sodium therapy.
Skeletal: muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgias.
Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances, anxiety, insomnia, depression.
Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.
Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.
Skin: alopecia, pruritus. A variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.
Reproductive: gynecomastia, loss of libido, erectile dysfunction.
Eye: progression of cataracts (lens opacities), ophthalmoplegia.
Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

Concomitant Therapy

Fluvastatin sodium has been administered concurrently with cholestyramine and nicotinic acid. No adverse reactions unique to the combination or in addition to those previously reported for this class of drugs alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. *(See WARNINGS: Skeletal Muscle.)*

OVERDOSAGE

The approximate oral LD_{50} is greater than 2 g/kg in mice and greater than 0.7 g/kg in rats.
The maximum single oral dose of Lescol® (fluvastatin sodium) capsules received by healthy volunteers was 80 mg. No clinically significant adverse experiences were seen at this dose. The maximum dose administered with an extended-release formulation was 640 mg for two weeks. This dose was not well tolerated and produced a variety of GI complaints and an increase in transaminase values (i.e., SGOT and SGPT).
There has been a single report of 2 children, one 2 years old and the other 3 years of age, either of whom may have possibly ingested fluvastatin sodium. The maximum amount of fluvastatin sodium that could have been ingested was 80 mg (4 × 20 mg capsules). Vomiting was induced by ipecac in both children and no capsules were noted in their emesis. Neither child experienced any adverse symptoms and both recovered from the incident without problems.
Should an accidental overdose occur, treat symptomatically and institute supportive measures as required. The dialyzability of fluvastatin sodium and of its metabolites in humans is not known at present.
Information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Regional Poison Control Centers are listed in the Physicians' Desk Reference®.*

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving Lescol® (fluvastatin sodium) or Lescol® XL (fluvastatin sodium) and should continue on this diet during treatment with Lescol or Lescol XL. (See NCEP Treatment Guidelines for details on dietary therapy.)
For patients requiring LDL-C reduction to a goal of ≥25%, the recommended starting dose is 40 mg as one capsule, 80 mg as one Lescol XL tablet administered as a single dose in the evening or 80 mg in divided doses of the 40 mg capsule given twice daily. For patients requiring LDL-C reduction to a goal of <25% a starting dose of 20 mg may be used. The recommended dosing range is 20-80 mg/day. Lescol or Lescol XL may be taken without regard to meals, since there are no apparent differences in the lipid-lowering effects of fluvastatin sodium administered with the evening meal or 4 hours after the evening meal. Since the maximal reductions in LDL-C of a given dose are seen within 4 weeks, periodic lipid determinations should be performed and dosage adjustment made according to the patient's response to therapy and established treatment guidelines. The therapeutic effect of Lescol or Lescol XL is maintained with prolonged administration.

Concomitant Therapy

Lipid-lowering effects on total cholesterol and LDL cholesterol are additive when immediate release Lescol is combined with a bile-acid binding resin or niacin. When administering a bile-acid resin (e.g., cholestyramine) and fluvastatin sodium, Lescol should be administered at bedtime, at least 2 hours following the resin to avoid a significant interaction due to drug binding to resin. *(See also ADVERSE REACTIONS: Concomitant Therapy.)*

Dosage in Patients with Renal Insufficiency

Since fluvastatin sodium is cleared hepatically with less than 6% of the administered dose excreted into the urine, dose adjustments for mild to moderate renal impairment are not necessary. Fluvastatin has not been studied at doses greater than 40 mg in patients with severe renal impairment; therefore caution should be exercised when treating such patients at higher doses.

HOW SUPPLIED

Lescol® (fluvastatin sodium) Capsules

20 mg
Brown and light brown imprinted twice with "◬" and "20" on one half and and the Lescol® (fluvastatin sodium) logo twice on the other half of the capsule.
Bottles of 30 capsules ..... (NDC 0078-0176-15)
Bottles of 100 capsules ..... (NDC 0078-0176-05)

40 mg
Brown and gold imprinted twice with "◬" and "40" on one half and "LESCOL" and the Lescol® (fluvastatin sodium) logo twice on the other half of the capsule.
Bottles of 30 capsules ..... (NDC 0078-0234-15)
Bottles of 100 capsules ..... (NDC 0078-0234-05)

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